10/828,479

EAST Search History (INCLUDING INTERFERENCE SEARCH)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	297	514/255.06	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2007/03/22 12:39
L2	73	l1 and (pyrazinoylguanidine or amiloride or (sodium adj channel))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2007/03/22 12:40
L3	73	l2 and method	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2007/03/22 12:40

STN TRANSCRIPT – 10/828,479

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NEWS	1		Web Page URLs for STN Seminar Schedule - N. America
NEWS	2		"Ask CAS" for self-help around the clock
NEWS	3	DEC 18	CA/CAplus pre-1967 chemical substance index entries enhanced with preparation role
NEWS	4	DEC 18	CA/CAplus patent kind codes updated
NEWS	5	DEC 18	MARPAT to CA/CAplus accession number crossover limit increased to 50,000
NEWS	6	DEC 18	MEDLINE updated in preparation for 2007 reload
NEWS	7	DEC 27	CA/CAplus enhanced with more pre-1907 records
NEWS	8	JAN 08	CHEMLIST enhanced with New Zealand Inventory of Chemicals
NEWS	9	JAN 16	CA/CAplus Company Name Thesaurus enhanced and reloaded
NEWS	10	JAN 16	IPC version 2007.01 thesaurus available on STN
NEWS	11	JAN 16	WPIDS/WPINDEX/WPIX enhanced with IPC 8 reclassification data
NEWS	12	JAN 22	CA/CAplus updated with revised CAS roles
NEWS	13	JAN 22	CA/CAplus enhanced with patent applications from India
NEWS	14	JAN 29	PHAR reloaded with new search and display fields
NEWS	15	JAN 29	CAS Registry Number crossover limit increased to 300,000 in multiple databases
NEWS	16	FEB 15	PATDPASPC enhanced with Drug Approval numbers
NEWS	17	FEB 15	RUSSIAPAT enhanced with pre-1994 records
NEWS	18	FEB 23	KOREAPAT enhanced with IPC 8 features and functionality
NEWS	19	FEB 26	MEDLINE reloaded with enhancements
NEWS	20	FEB 26	EMBASE enhanced with Clinical Trial Number field
NEWS	21	FEB 26	TOXCENTER enhanced with reloaded MEDLINE
NEWS	22	FEB 26	IFICDB/IFIPAT/IFIUDB reloaded with enhancements
NEWS	23	FEB 26	CAS Registry Number crossover limit increased from 10,000 to 300,000 in multiple databases
NEWS	24	MAR 15	WPIDS/WPIX enhanced with new FRAGHITSTR display format
NEWS	25	MAR 16	CASREACT coverage extended
NEWS	26	MAR 20	MARPAT now updated daily
NEWS	27	MAR 22	LWPI reloaded

NEWS EXPRESS NOVEMBER 10 CURRENT WINDOWS VERSION IS V8.01c, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 25 SEPTEMBER 2006.

NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS LOGIN	Welcome Banner and News Items
NEWS IPC8	For general information regarding STN implementation of IPC 8
NEWS X25	X.25 communication option no longer available

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* * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 14:01:47 ON 22 MAR 2007

=> file reg
COST IN U.S. DOLLARS — SINCE FILE ENTRY: 0.21 — TOTAL SESSION: 0.21
FULL ESTIMATED COST

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STRUCTURE FILE UPDATES: 20 MAR 2007 HIGHEST RN 927800-28-0
DICTIONARY FILE UPDATES: 20 MAR 2007 HIGHEST RN 927800-28-0

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http://www.cas.org/ONLINE/UG/regprops.html

=>
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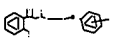

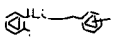

chain nodes :
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ring nodes :
1 2 3 4 5 6 17 18 19 20 21 22
chain bonds :
5-10 6-7 7-8 10-11 10-12 12-13 13-14 13-15 15-16 16-26 17-26
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 17-22 17-18 18-19 19-20 20-21 21-22
exact/norm bonds :
6-7 10-11 10-12 12-13 13-14 13-15 15-16 16-26
exact bonds :
5-10 7-8 17-26
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6 17-22 17-18 18-19 19-20 20-21 21-22
isolated ring systems :
containing 1 : 17 :

G1:C,O,N

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:CLASS 8:CLASS 10:CLASS 11:CLASS 12:CLASS 13:CLASS 14:CLASS 15:CLASS 16:CLASS 17:Atom 18:Atom 19:Atom 20:Atom 21:Atom 22:Atom 24:CLASS 25:Atom 26:CLASS

L1 STRUCTURE UPLOADED

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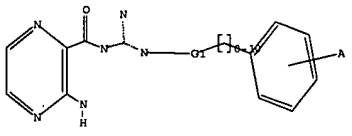
L1 STR



G1 C,O,N

Structure attributes must be viewed using STN Express query preparation.

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FULL SCREEN SEARCH COMPLETED - 380 TO ITERATE

100.0% PROCESSED 380 ITERATIONS 272 ANSWERS
SEARCH TIME: 00.00.01

L2 272 SEA SSS FUL L1

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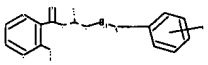

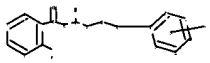

chain nodes :
7 8 10 11 12 13 14 15 16 17 27
ring nodes :
1 2 3 4 5 6 18 19 20 21 22 23
chain bonds :
5-10 6-7 7-8 10-11 10-12 12-13 13-14 13-15 15-16 16-17 17-18
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 18-23 18-19 19-20 20-21 21-22 22-23
exact/norm bonds :
6-7 10-11 10-12 12-13 13-14 13-15 15-16 16-17 17-18
exact bonds :
5-10 7-8
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6 18-23 18-19 19-20 20-21 21-22 22-23
isolated ring systems :
containing 1 : 18 :

G1:C,O,N

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:CLASS 8:CLASS 10:CLASS 11:CLASS 12:CLASS 13:CLASS 14:CLASS 15:CLASS 16:CLASS 17:CLASS 18:Atom 19:Atom 20:Atom 21:Atom 22:Atom 23:Atom 27:CLASS 28:Atom

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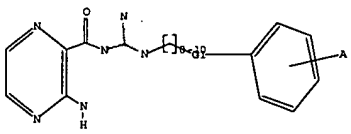

G1 C,O,N

Structure attributes must be viewed using STN Express query preparation.

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100.0% PROCESSED 663 ITERATIONS 283 ANSWERS
SEARCH TIME: 00.00.01

L4 283 SEA SSS FUL L3

=> s l3 or l4
L4 MAY NOT BE USED HERE
The L-number entered was not created by a STRUCTURE or SCREEN command.

=> s l2 or l4
L5 283 L2 OR L4

=> file caplus
COST IN U.S. DOLLARS SINCE FILE ENTRY 348.70 TOTAL SESSION 348.91

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FILE LAST UPDATED: 21 Mar 2007 (20070321/ED)

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=> s l5
L6 122 L5

=> d 1-122 ibib abs hitstr

L6 ANSWER 1 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2007:146829 CAPLUS
DOCUMENT NUMBER: 146:229606
TITLE: Preparation of new capped pyrazinoylguanidine-containing amino acid derivatives as sodium channel blockers
INVENTOR(S): Johnson, Michael R.; Molino, Bruce F.; Sargent, Bruce; Zhang, Jianzhong
PATENT ASSIGNEE(S): Parion Sciences, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 30pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2007032509	A1	20070208	US 2005-195758	20050803
WO 2007018640	A1	20070215	WO 2006-US15957	20060427

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2005-195758 A 20050803
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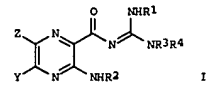

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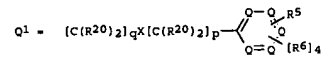
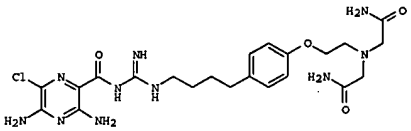




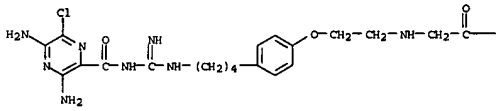
II

AB Title compds. [I; Z = H, halo, CF3, alkyl, (un)substituted Ph, alkylthio, phenylalkylthio, alkylsulfonyl, phenylalkylsulfonyl; Y = H, OH, SH, alkoxy, alkylthio, halo, alkyl, amino, (un)substituted aryl; R1 = H, alkyl; R2 = R7, (CH2)mOR8, (CH2)mNR7R10, (CH2CH2O)mR8, etc.; R3, R4 = independently H, alkyl, hydroxyalkyl, phenylalkyl, pyridylalkyl, Q1, etc.; R20 = R7, (CH2)mOR8, (CH2)mNR7R10, OSO3H, etc.; X = O, NR10, CO, CH(OH), C:NR10, CHNR7R10, bond; R5 = O(CH2)nNH(CH2)mCR10[(CH2)mR9][(CH2)mR9], SO2(CH2)mNR13[(CH2)mCO2R13] etc.; R6 = R7, OR8, N(R7)2, (CH2)mOR8, OSO3H, etc.; R7 = H, alkyl, (un)substituted Ph, etc.; R8 = H, alkyl, COR11, glucuronide, 2-tetrahydropyranyl, etc.; R9 = CO2R13, SO2CH2R13, oxazolidinedione, etc.; R10 = H, SO2Me, CO2R13, COR13, etc.; R11 = alkyl; R13 = R7, R10; Q = CR5, CR6, N; m = 1-7; n = 0-7; q, p = independently 0-10; with provisos; their enantiomers, diastereomers and racemates, and their pharmaceutically acceptable salts] were prepared as sodium channel blockers. Thus, II was prepared by alkylation of [4-[4-(2-aminoethoxy)phenyl]butyl]carbamic acid tert-Bu ester with 2-bromoethyl acetate, ammonolysis of the diester, removal of the tert-butoxycarbonyl group, and reaction of the amine bistrifluoroacetate with 1-[(3,5-diamino-6-chloropyrazin-2-yl)carbonyl]-2-methylisothiourea hydroiodide. II showed 77 times the activity of amiloride in a screen for epithelial sodium channel blocking activity.

IT 924279-09-4P, 2-[[2-[4-[4-[N'-[(3,5-Diamino-6-chloropyrazin-2-yl)carbonyl]guanidino]butyl]phenoxy]ethyl]amino]acetamide
924279-13-0P, 2-[(Carbamoylmethyl)[2-[4-[4-[N'-[(3,5-diamino-6-chloropyrazin-2-yl)carbonyl]guanidino]butyl]phenoxy]ethyl]amino]acetamide
924279-18-5P, [[2-[4-[4-[N'-[(3,5-Diamino-6-chloropyrazin-2-yl)carbonyl]guanidino]butyl]phenoxy]ethyl]amino]aceticacid
924279-21-0P, [(Carboxymethyl)[2-[4-[4-[N'-[(3,5-diamino-6-chloropyrazin-2-yl)carbonyl]guanidino]butyl]phenoxy]ethyl]amino]acetic acid 924279-24-3P 924279-27-6P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; preparation of capped pyrazinoylguanidine-containingamino acid
derivs. as sodium channel blockers)

RN 924279-09-4 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

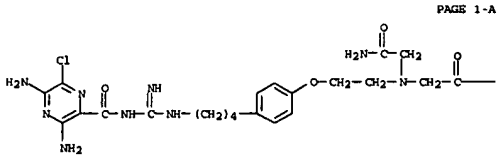
PAGE 1-A



PAGE 1-B

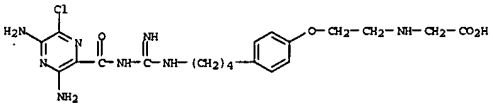
RN 924279-13-0 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

PAGE 1-A



PAGE 1-B

RN 924279-18-5 CAPLUS
CN INDEX NAME NOT YET ASSIGNED



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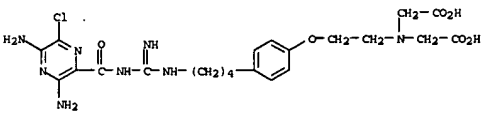

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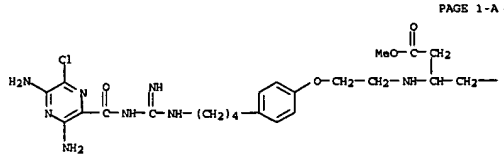
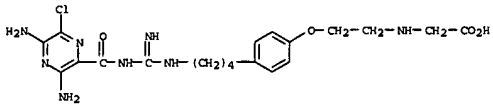
CN INDEX NAME NOT YET ASSIGNED

PAGE 1-A



●2 HCl

RN 924279-27-6 CAPLUS
CN INDEX NAME NOT YET ASSIGNED



●2 HCl

L6 ANSWER 2 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2007:88134 CAPLUS
DOCUMENT NUMBER: 146:184493
TITLE: Methods of reducing risk of infection from airborne pathogens by administration of soluble amide and ester pyrazinoylguanidine sodium channel blockers
INVENTOR(S): Johnson, Michael R.
PATENT ASSIGNEE(S): Parion Sciences, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 59pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2007021439	A1	20070125	US 2005-188673	20050725
PRIORITY APPLN. INFO.:			US 2005-188673	20050725

OTHER SOURCE(S): MARPAT 146:184493
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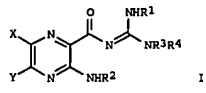
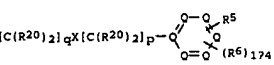
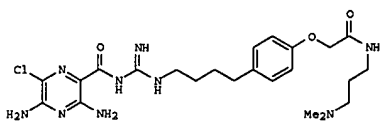




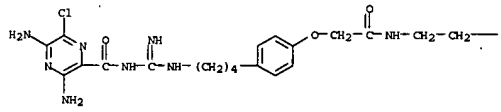


AB Prophylactic treatment methods are provided comprising administering of a sodium channel blocker I [X = H, halo, CF3, alkyl, (substituted) Ph, alkylthio, phenylalkylthio, alkylsulfonyl, phenylalkylsulfonyl; Y = H, OH, SH, alkoxy, alkylthio, halo, alkyl, (substituted) aryl, amino; R1 = H, alkyl; R2 = R7, (CH2)mOR8, (CH2)mNR7R10, (CH2CH2O)nR8, etc.; R3, R4 = H, alkyl, hydroxyalkyl, phenylalkyl, pyridylalkyl, Q1, etc.; R20 = R7, (CH2)nOR8, (CH2)nNR7R10, OSO3H, etc.; X = O, NR10, CO, CH(OH), C:NR10, CHNR7R10, bond; R5 = (CH2)nCO2R13, Het(CH2)mCO2R13, etc.; R6 = R5, R7, OR8, N(R7)2, (CH2)mOR8, OSO3H, etc.; R7 = H, alkyl, (substituted) Ph, etc.; R8 = H, alkyl, COR11, glucuronide, 2-tetrahydropyranyl, etc.; R10 = H, SO2Me, CO2R7, COR7, etc.; R11 = alkyl; R13 = H, R7, R10, (CH2)mNR7R10, etc.; R20 = R7, (CH2)nOR8, (CH2)nNR7R10, OSO3H, etc.; Het = NR7, NR10, S, SO, SO2, O, SO2NH, CONR7, etc.; Q = CR5, CR5, N; m = 1-7; n = 0-7; q, p = 0-10; with provisos] or a pharmaceutically acceptable salt thereof for protection of individuals and/or populations against infection from airborne pathogens. In particular, prophylactic treatment methods are provided comprising administering a sodium channel blocker I or a pharmaceutically acceptable salt thereof to one or more members of a population at risk of exposure to or already exposed to one or more airborne pathogens, either from natural sources or from intentional release of pathogens into the environment. Thus, coupling of [4-[4-[[(phenylmethoxy]carbonyl]amino]butyl]phenoxy]acetimidic acid with N,N-dimethyl-1,3-diaminopropane, hydrogenolysis, reaction with 1-[(3,5-diamino-6-chloropyrazin-2-yl)carbonyl]-2-methylisothiourea hydroiodide, and acidulation with methanesulfonic acid gave pyrazinoylguanidine II•2MeSO3H. Pyrazinoylguanidine II•2MeSO3H showed 173 times the activity of amiloride in a screen for epithelial sodium channel blocking activity.

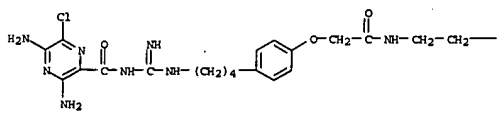
IT 876130-93-7P 876130-96-0P 876130-99-3P
876131-07-6P 876131-08-7P 876131-09-8P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of soluble amide and ester pyrazinoylguanidine sodium channel blockers and their use for reducing risk of infection from airborne pathogens)

RN 876130-93-7 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[2-[[2-(dimethylamino)ethyl]amino]-2-oxoethoxy]phenyl]butyl]amino]iminomethyl]-

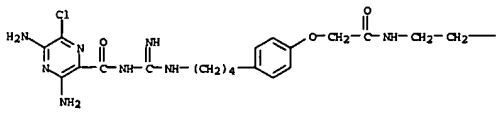
(9CI) (CA INDEX NAME)



RN 876130-96-0 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[2-[[2-[bis(2-hydroxyethyl)amino]ethyl]amino]-2-oxoethoxy]phenyl]butyl]amino]iminomethyl]-6-chloro- (9CI) (CA INDEX NAME)



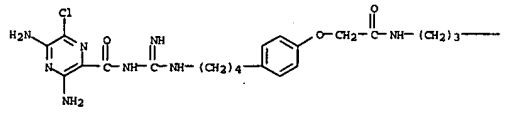
RN 876130-99-3 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[2-[(2-aminoethyl)amino]-2-oxoethoxy]phenyl]butyl]amino]iminomethyl]-6-chloro-(9CI) (CA INDEX NAME)



RN 876131-07-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[2-[[3-(dimethylamino)propyl]amino]-2-oxoethoxy]phenyl]butyl]amino]iminomethyl]-, dimethanesulfonate (9CI) (CA INDEX NAME)

CM 1

CRN 876131-01-0
CMF C23 H34 Cl N9 O3



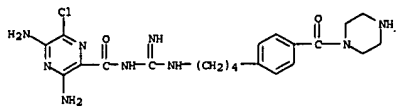
CM 2

CRN 75-75-2
CMF C H4 O3 S

RN 876131-08-7 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[4-[4-(1-piperazinylcarbonyl)phenyl]butyl]amino]methyl]-,dimethanesulfonate (9CI) (CA INDEX NAME)

CM 1

CRN 876130-98-2
CMF C21 H28 Cl N9 O2

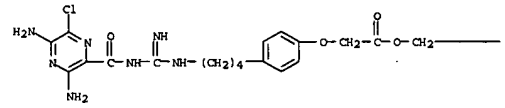


CM 2

CRN 75-75-2
CMF C H4 O3 S

RN 876131-09-8 CAPLUS
CN Acetic acid, [4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]imino methyl]amino]butyl]phenoxy]-, 4-piperidinylmethyl ester, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A

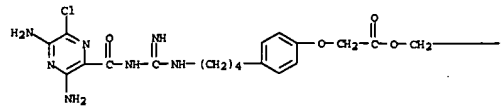


●2 HCl

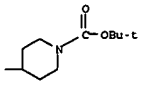
PAGE 1-B

IT 876131-39-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of soluble amide and ester pyrazinoylguanidine sodium channel blockers and their use for reducing risk of infection from airborne pathogens)
RN 876131-39-4 CAPLUS
CN 1-Piperidinecarboxylic acid, 4-[[[[4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenoxy]acetyl]oxy]methyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

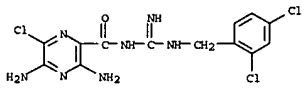
PAGE 1-A



PAGE 1-B



L6 ANSWER 3 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:956390 CAPLUS
DOCUMENT NUMBER: 145:284186
TITLE: Intrasperm Ca2+ modulation and human ejaculated sperm viability: influence of miconazole, clotrimazole and loperamide
AUTHOR(S): Gulati, Abhishek; Tiwary, Ashok K.; Jain, Subheet; Moudgil, Pranab; Gupta, Anshu
CORPORATE SOURCE: Department of Pharmaceutical Sciences and Drug Research, Punjabi University, Patiala, 147 002, India
SOURCE: Journal of Pharmacy and Pharmacology (2006), 58(8), 1145-1151
CODEN: JPPMAB; ISSN: 0022-3573
PUBLISHER: Pharmaceutical Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Elevation of intrasperm Ca2+ is reported to influence viability of ejaculated spermatozoa. Human spermatozoa possess inositol triphosphate (IP3)-sensitive Ca2+ stores, which can be targeted for increasing intrasperm Ca2+ level. The influence of agents affecting Ca2+ homeostasis has been investigated. Miconazole nitrate, clotrimazole and loperamide hydrochloride produced a dose- and time-dependent decrease in viability, each requiring resp. 0.5, 1.0 and 1.0 mM for producing death of all sperm cells immediately upon addition to ejaculated human semen samples. The reduction
in sperm viability was accompanied by elevation of intrasperm Ca2+ and was not affected by presence or absence of extracellular Ca2+. Significantly ($P < 0.05$) less time was required for producing complete loss of sperm viability and increasing intrasperm Ca2+ when any of these drugs was added to sperm cells previously treated with selected agents affecting Ca2+ homeostasis. This enhanced spermicidal activity of miconazole, clotrimazole and loperamide appeared to be due to further mobilization of Ca2+ from partially depleted intrasperm Ca2+ stores. Synergism of spermicidal activity and intrasperm Ca2+ elevation by miconazole or clotrimazole was observed when Ca2+ efflux from sperm cells was simultaneously inhibited by 2',4'-dichlorobenzamil hydrochloride, a Na+-Ca2+ exchange inhibitor. The spermicidal activity of miconazole, clotrimazole or loperamide due to elevation of intrasperm Ca2+ and its synergism, therefore, has great potential for exploitation of these drugs as contact spermicides.
IT 2088-58-6, 2', 4'-Dichlorobenzamil hydrochloride
RL: PAC (Pharmacological activity); BIOL (Biological study)
(intrasperm calcium modulation and human ejaculated sperm viability)
RN 2088-58-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2,4-dichlorophenyl)methyl]amino]iminomethyl]-,monohydrochloride (9CI) (CA INDEX NAME)



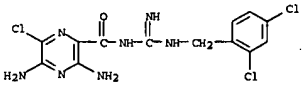
● HCl

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

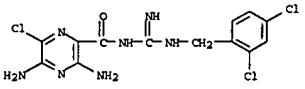
L6 ANSWER 4 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:768559 CAPLUS
DOCUMENT NUMBER: 145:202854
TITLE: Small molecules that reduce fungal growth
INVENTOR(S): Johnson, Douglas I.; Toenjes, Kurt A.
PATENT ASSIGNEE(S): University of Vermont and State Agricultural College, USA
SOURCE: PCT Int. Appl., 79pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006081327	A2	20060803	WO 2006-US2711	20060125
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
US 2006194769	A1	20060831	US 2006-340418	20060125

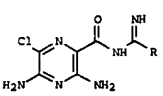
PRIORITY APPLN. INFO.: US 2005-646967P P 20050125
AB The present invention relates to methods for reducing the growth of a fungus with an anti-fungal small mol. Methods for reducing fungal cell growth in a subject with an anti-fungal small mol. and related compns. are provided. Topical lotion formulations of an anti-fungal small mol. and a topical carrier are also provided.
IT 90689-42-2 90689-42-2L, analogs
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(small mols. that reduce fungal growth)
RN 90689-42-2 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



RN 90689-42-2 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



L6 ANSWER 5 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:593381 CAPLUS
DOCUMENT NUMBER: 145:211000
TITLE: Design, Synthesis, and Structure-Activity Relationships of Novel 2-Substituted Pyrazinoylguanidine Epithelial Sodium Channel Blockers: Drugs for Cystic Fibrosis and Chronic Bronchitis
AUTHOR(S): Hirsh, Andrew J.; Molino, Bruce F.; Zhang, Jianzhong; Astakhova, Nadezhda; Geiss, William B.; Sargent, Bruce J.; Swenson, Brian D.; Usyatinsky, Alexander; Wyle, Michael J.; Boucher, Richard C.; Smith, Rick T.; Zamurs, Andra; Johnson, M. Ross
CORPORATE SOURCE: Parion Sciences Inc., Durham, NC, 27713, USA
SOURCE: Journal of Medicinal Chemistry (2006), 49(14), 4098-4115
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



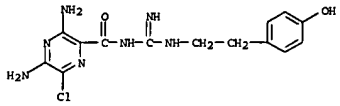
I

AB Amiloride, the prototypical epithelial sodium channel (ENaC) blocker, has been administered with limited success as aerosol therapy for improving pulmonary function in patients with the genetic disorder cystic fibrosis. This study was conducted to synthesize and identify more potent, less reversible ENaC blockers, targeted for aerosol therapy and possessing

minimal systemic renal activity. A series of novel 2-substituted acylguanidine analogs of amiloride were synthesized and evaluated for potency and reversibility on bronchial ENaC. All compds. tested were more potent and less reversible at blocking sodium-dependent short-circuit current than amiloride. Compds. I [R = NH(CH2)4C6H4O(CH2)2OH-4, NH(CH2)4C6H4O(CH2)3OH-4, NH(CH2)4C6H4OCH2CH(OH)CH2OH-4 (both R and S isomers)] showed the greatest potency on ENaC with IC50 values below 10 nM. A regioselective difference in potency was found, whereas no stereospecific difference in potency on ENaC was displayed. Lead compound I [R = NH(CH2)4C6H4OCH2CH(OH)CH2OH-4 (racemic)] was 102-fold more potent and 5-fold less reversible than amiloride and displayed the lowest IC50 value ever reported for an ENaC blocker.

IT 905292-80-0
RL: PAC (Pharmacological activity); BIOL (Biological study)
(design, synthesis, and structure-activity relationships of 2-substituted pyrazinoylguanidine epithelial sodium channel blockers as potential drugs for cystic fibrosis and chronic bronchitis)

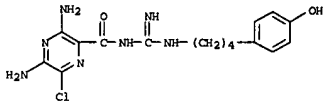
RN 905292-80-0 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[2-(4-hydroxyphenyl)ethyl]amino]iminomethyl]-,monohydrochloride (9CI) (CA INDEX NAME)



● HCl

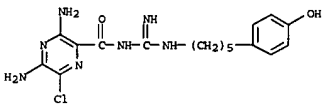
IT 583825-15-4P 587879-55-8P 905292-88-8P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(design, synthesis, and structure-activity relationships of 2-substituted pyrazinoylguanidine epithelial sodium channel blockers as potential drugs for cystic fibrosis and chronic bronchitis)

RN 583825-15-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-(4-hydroxyphenyl)butyl]amino]iminomethyl]-,monohydrochloride (9CI) (CA INDEX NAME)



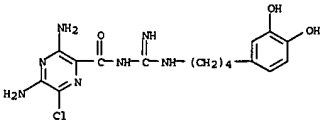
● HCl

RN 587879-55-8 CAPLUS



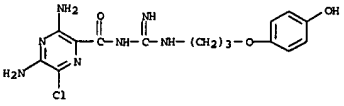
● HCl

RN 583825-19-8 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-(3,4-dihydroxyphenyl)butyl]amino]iminomethyl]-,monohydrochloride (9CI) (CA INDEX NAME)



● HCl

RN 583825-33-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[3-(4-hydroxyphenoxy)propyl]amino]iminomethyl]-,monohydrobromide (9CI) (CA INDEX NAME)



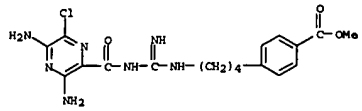
● HBr

RN 587879-54-7 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-(2,3-dihydroxypropoxy)phenyl]butyl]amino]iminomethyl]-,monomethanesulfonate (salt) (9CI) (CA INDEX NAME)

CM 1

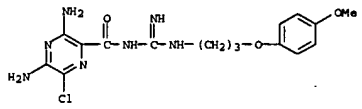
CRN 587879-32-1
CMF C19 H26 Cl N7 O4

CN Benzoic acid, 4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]-, methyl ester, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

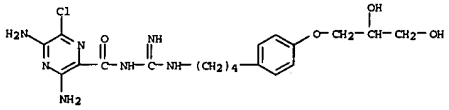
RN 905292-88-8 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[3-(4-methoxyphenoxy)propyl]amino]methyl]-,monohydrochloride (9CI) (CA INDEX NAME)



● HCl

IT 583825-17-6P 583825-19-8P 583825-33-6P
587879-54-7P 587879-56-9P 587879-64-9P
587879-70-7P 905292-81-1P 905292-82-2P
905292-83-3P 905292-84-4P 905292-85-5P
905292-86-6P 905292-87-7P 905292-89-9P
905292-91-3P 905292-92-4P 905292-93-5P
905292-94-6P 905292-95-7P 905292-96-8P
905292-97-9P 905292-98-0P 905292-99-1P
905293-00-7P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(design, synthesis, and structure-activity relationships of 2-substituted pyrazinoylguanidine epithelial sodium channel blockers as potential drugs for cystic fibrosis and chronic bronchitis)

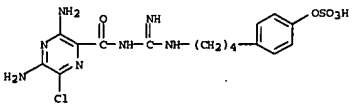
RN 583825-17-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[5-(4-hydroxyphenyl)pentyl]amino]iminomethyl]-,monohydrochloride (9CI) (CA INDEX NAME)



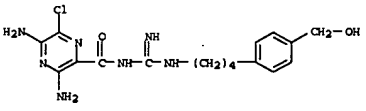
CM 2

CRN 75-75-2
CMF C H4 O3 S

RN 587879-56-9 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[4-[4-(sulfooxy)phenyl]butyl]amino]methyl]-(9CI) (CA INDEX NAME)

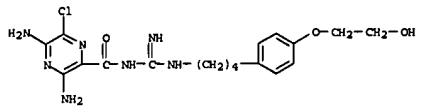


RN 587879-64-9 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-(hydroxymethyl)phenyl]butyl]amino]iminomethyl]-,monohydrochloride (9CI) (CA INDEX NAME)



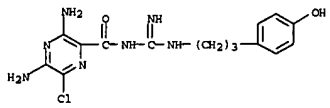
● HCl

RN 587879-70-7 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-(2-hydroxyethoxy)phenyl]butyl]amino]iminomethyl]-,monohydrochloride (9CI) (CA INDEX NAME)



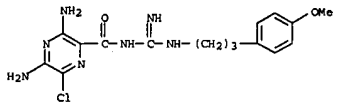
● HCl

RN 905292-81-1 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[3-(4-hydroxyphenyl)propyl]amino]iminomethyl]-,monohydrochloride (9CI) (CA INDEX NAME)



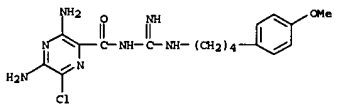
● HCl

RN 905292-82-2 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[3-(4-methoxyphenyl)propyl]amino]methyl]-,monohydrochloride (9CI) (CA INDEX NAME)



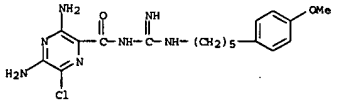
● HCl

RN 905292-83-3 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-(3-hydroxyphenyl)butyl]amino]iminomethyl]-,monohydrochloride (9CI) (CA INDEX NAME)



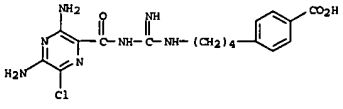
● HCl

RN 905292-87-7 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[5-(4-methoxyphenyl)pentyl]amino]methyl]-,monohydrochloride (9CI) (CA INDEX NAME)



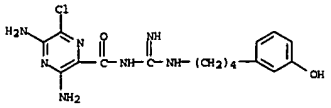
● HCl

RN 905292-89-9 CAPLUS
CN Benzoic acid, 4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]imino methyl]amino]butyl]-, monohydrochloride (9CI) (CA INDEX NAME)



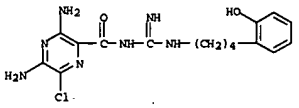
● HCl

RN 905292-91-3 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-(3-hydroxypropoxy)phenyl]butyl]amino]iminomethyl]-,monohydrochloride (9CI) (CA INDEX NAME)



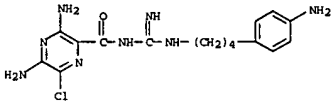
● HCl

RN 905292-84-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-(2-hydroxyphenyl)butyl]amino]iminomethyl]-,monohydrochloride (9CI) (CA INDEX NAME)



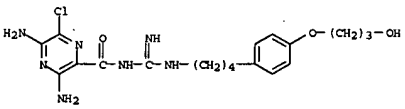
● HCl

RN 905292-85-5 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-(4-aminophenyl)butyl]amino]iminomethyl]-6-chloro-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

RN 905292-86-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[4-(4-methoxyphenyl)butyl]amino]methyl]-,monohydrochloride (9CI) (CA INDEX NAME)



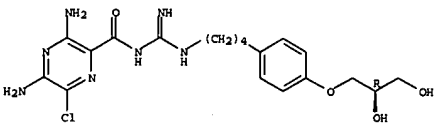
● HCl

RN 905292-92-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[(2R)-2,3-dihydroxypropoxy]phenyl]butyl]amino]iminomethyl]-,monomethanesulfonate (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 587879-35-4
CMF C19 H26 Cl N7 O4

Absolute stereochemistry. Rotation (-).



CM 2

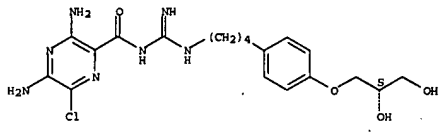
CRN 75-75-2
CMF C H4 O3 S

RN 905292-93-5 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[(2S)-2,3-dihydroxypropoxy]phenyl]butyl]amino]iminomethyl]-,monomethanesulfonate (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 587879-36-5
CMF C19 H26 Cl N7 O4

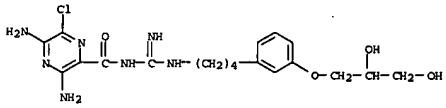
Absolute stereochemistry. Rotation (+).



CM 2

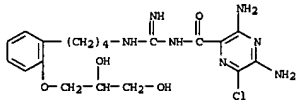
CRN 75-75-2
CMF C H4 O3 S

RN 905292-94-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[3-(2,3-dihydroxypropoxy)phenyl]butyl]amino]iminomethyl]-,monohydrochloride (9CI) (CA INDEX NAME)

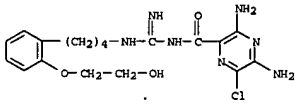


● HCl

RN 905292-95-7 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[2-(2,3-dihydroxypropoxy)phenyl]butyl]amino]iminomethyl]-,monohydrochloride (9CI) (CA INDEX NAME)



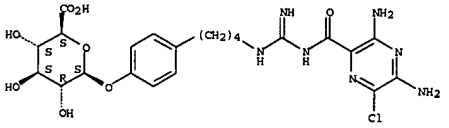
● HCl



● HCl

RN 905293-00-7 CAPLUS
CN β-D-Glucopyranosiduronic acid, 4-[4-[[[[(3,5-diamino-6-chloropyrazinyl]carbonyl]amino]iminomethyl]amino]butyl]phenyl monosodium salt (9CI) (CA INDEX NAME)

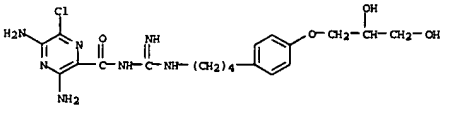
Absolute stereochemistry.



● Na

IT 587879-32-1P 587879-35-4P 587879-36-5P
587879-60-5P 587880-07-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(design, synthesis, and structure-activity relationships of 2-substituted pyrazinoylguanidine epithelial sodium channel blockers as potential drugs for cystic fibrosis and chronic bronchitis)

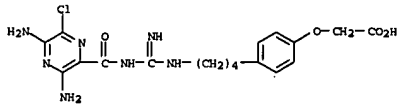
RN 587879-32-1 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-(2,3-dihydroxypropoxy)phenyl]butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



RN 587879-35-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[(2R)-2,3-dihydroxypropoxy]phenyl]butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)

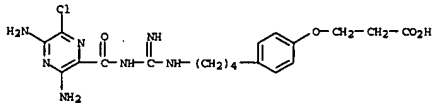
Absolute stereochemistry. Rotation (-).

RN 905292-96-8 CAPLUS
CN Acetic acid, [4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenoxy]-, monohydrochloride (9CI) (CA INDEX NAME)



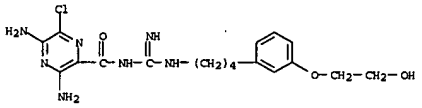
● HCl

RN 905292-97-9 CAPLUS
CN Propanoic acid, 3-[4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenoxy]-, monohydrochloride (9CI) (CA INDEX NAME)



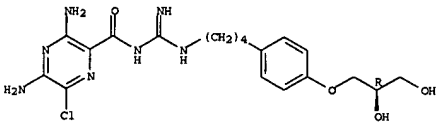
● HCl

RN 905292-98-0 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[3-(2-hydroxyethoxy)phenyl]butyl]amino]iminomethyl]-,monohydrochloride (9CI) (CA INDEX NAME)



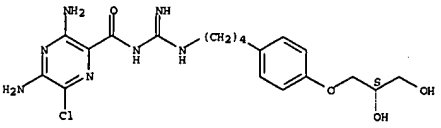
● HCl

RN 905292-99-1 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[2-(2-hydroxyethoxy)phenyl]butyl]amino]iminomethyl]-,monohydrochloride (9CI) (CA INDEX NAME)



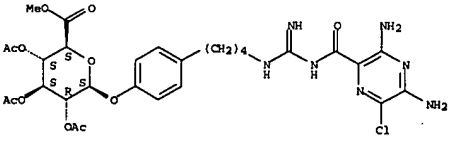
RN 587879-36-5 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[(2S)-2,3-dihydroxypropoxy]phenyl]butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

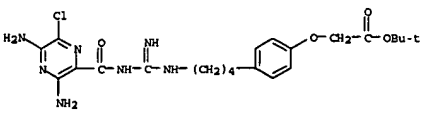


RN 587879-60-5 CAPLUS
CN β-D-Glucopyranosiduronic acid, 4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenyl methyl ester, 2,3,4-triacetate (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 587880-07-7 CAPLUS
CN Acetic acid, [4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenoxy]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



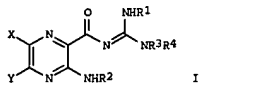
REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 6 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:170470 CAPLUS
DOCUMENT NUMBER: 144:233101
TITLE: Preparation of soluble amide and ester pyrazinoylguanidines as sodium channel blockers.
INVENTOR(S): Johnson, Michael R.
PATENT ASSIGNEE(S): Parion Sciences, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 74 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2006040954	A1	20060223	US 2004-920391	20040818
WO 2006022935	A1	20060302	WO 2005-US17740	20050520

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2004-920391 A 20040818
OTHER SOURCE(S): MARPAT 144:233101
GI



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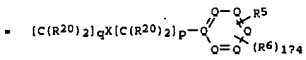
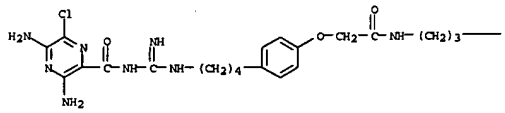


AB Title compds. [I; X = H, halo, CF3, alkyl, (substituted) Ph, alkylthio, phenylalkylthio, alkylsulfonyl, phenylalkylsulfonyl; Y = H, OH, SH, alkoxy, alkylthio, halo, alkyl, (substituted) aryl, amino; R1 = H, alkyl; R2 = R7, (CH2)mOR8, (CH2)mNR7R10, (CH2CH2O)mR8, etc.; R3, R4 = H, alkyl, hydroxyalkyl, phenylalkyl, pyridylalkyl, Q1, etc.; R20 = R7, (CH2)nOR8, (CH2)nNR7R10, OSO3H, etc.; X = O, NR10, CO, CH(OH), C:NR10, CHNR7R10, bond; R5 = (CH2)nCO2R13, Het(CH2)mCO2R13, etc.; R6 = R5, R7, OR8, N(R7)2, (CH2)mOR8, OSO3H, etc.; R7 = H, alkyl, (substituted) Ph, etc.; R8 = H, alkyl, COR11, glucuronide, 2-tetrahydropyranyl, etc.; R10 = H, SO2Me, CO2R7, COR7, etc.; R11 = alkyl; R13 = H, R7, R10, (CH2)mNR7R10, etc.; R20 = R7, (CH2)nOR8, (CH2)nNR7R10, OSO3H, etc.; Het = NR7, NR10, S, SO, SO2, O, SO2NH, CONR7, etc.; Q = CR5, CR5, N; m = 1-7; n = 0-7; q, p = 0-10; with provisos], were prepared Thus, [4-[4-[N'-(3,5-diamino-6-chloropyrazine-2-carbonyl)guanidino]butyl]phenoxy]aceticacid piperidin-4-ylmethyl ester dihydrochloride (preparation given) showed 189 times the activity of amiloride in a screen for epithelial sodium channel blocking activity.

IT 876131-01-0P 876131-04-3P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(claimed compound; preparation of soluble amide and ester pyrazinoylguanidines as sodium channel blockers)

RN 876131-01-0 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[2-[[3-(dimethylamino)propyl]amino]-2-oxoethoxy]phenyl]butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)

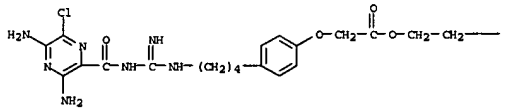
PAGE 1-A



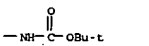
PAGE 1-B

RN 876131-04-3 CAPLUS
CN Acetic acid, [4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenoxy]-, 2-[[(1,1-dimethylethoxy)carbonyl]amino]ethyl ester (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 1-B



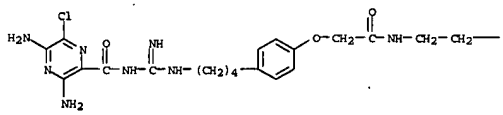
IT 876130-94-8P 876130-97-1P 876130-98-2P
876131-00-9P 876131-02-1P 876131-03-2P
876131-05-4P 876131-06-5P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(claimed compound; preparation of soluble amide and ester pyrazinoylguanidines as sodium channel blockers)

RN 876130-94-8 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[2-[[2-(dimethylamino)ethyl]amino]-2-oxoethoxy]phenyl]butyl]amino]iminomethyl]-, dimethanesulfonate (9CI) (CA INDEX NAME)

CM 1

CRN 876130-93-7
CMF C22 H32 Cl N9 O3

PAGE 1-A



PAGE 1-B

CM 2

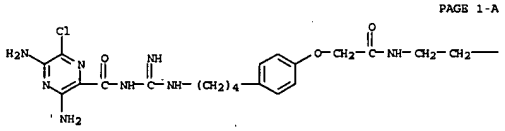
CRN 75-75-2
CMF C H4 O3 S

RN 876130-97-1 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[2-[[2-[bis(2-hydroxyethyl)amino]ethyl]amino]-2-oxoethoxy]phenyl]butyl]amino]iminomethyl]-6-chloro-, dimethanesulfonate (salt) (9CI) (CA INDEX NAME)

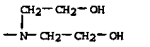
CM 1

CRN 876130-96-0
CMF C24 H36 Cl N9 O5

PAGE 1-A



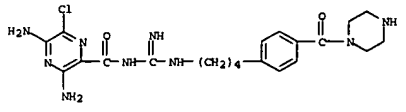
PAGE 1-B



CM 2

CRN 75-75-2
CMF C H4 O3 S

RN 876130-98-2 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[4-[4-(1-piperazinylcarbonyl)phenyl]butyl]amino]methyl]-(9CI) (CA INDEX NAME)

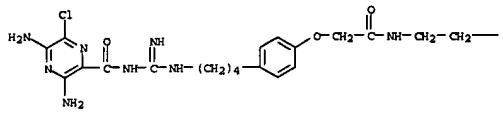


RN 876131-00-9 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[2-[(2-aminoethyl)amino]-2-oxoethoxy]phenyl]butyl]amino]iminomethyl]-6-chloro-, dimethanesulfonate (9CI) (CA INDEX NAME)

CM 1

CRN 876130-99-3
CMF C20 H28 Cl N9 O3

PAGE 1-A



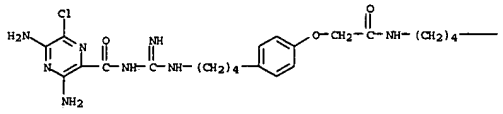
PAGE 1-B

CM 2

CRN 75-75-2
CMF C H4 O3 S

RN 876131-02-1 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[2-[[4-(dimethylamino)butyl]amino]-2-oxoethoxy]phenyl]butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)

PAGE 1-A



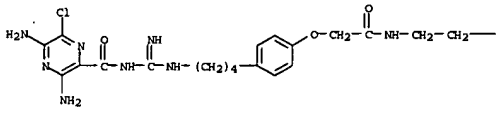
PAGE 1-B

RN 876131-03-2 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[4-[4-[2-oxo-2-(1-piperazinyl)ethoxy]phenyl]butyl]amino]methyl]-(9CI) (CA INDEX NAME)

IT 876130-93-7P 876130-96-0P 876130-99-3P
876131-07-6P 876131-08-7P 876131-09-8P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of soluble amide and ester pyrazinoylguanidines as sodium channel blockers)

RN 876130-93-7 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[2-[[2-(dimethylamino)ethyl]amino]-2-oxoethoxy]phenyl]butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)

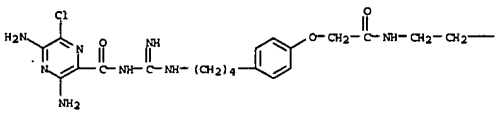
PAGE 1-A



PAGE 1-B

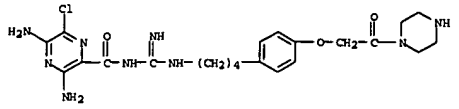
RN 876130-96-0 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[2-[[2-[bis(2-hydroxyethyl)amino]ethyl]amino]-2-oxoethoxy]phenyl]butyl]amino]iminomethyl]-6-chloro- (9CI) (CA INDEX NAME)

PAGE 1-A



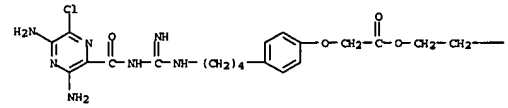
PAGE 1-B

RN 876130-99-3 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[2-[(2-aminoethyl)amino]-2-oxoethoxy]phenyl]butyl]amino]iminomethyl]-6-chloro-(9CI) (CA INDEX NAME)



RN 876131-05-4 CAPLUS
CN Acetic acid, [4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenoxy]-, 2-(1-piperidinyl)ethyl ester (9CI) (CA INDEX NAME)

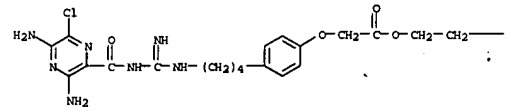
PAGE 1-A



PAGE 1-B

RN 876131-06-5 CAPLUS
CN Acetic acid, [4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenoxy]-, 2-aminoethyl ester, dihydrochloride (9CI) (CA INDEX NAME)

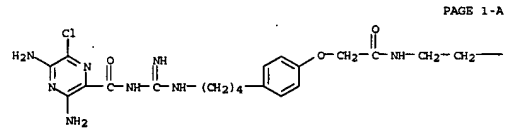
PAGE 1-A



●2 HCl

PAGE 1-B

PAGE 1-A



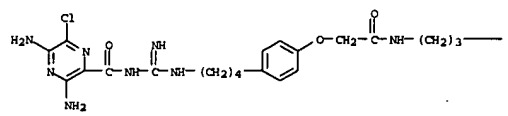
PAGE 1-B

RN 876131-07-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[2-[[3-(dimethylamino)propyl]amino]-2-oxoethoxy]phenyl]butyl]amino]iminomethyl]-, dimethanesulfonate (9CI) (CA INDEX NAME)

CM 1

CRN 876131-01-0
CMF C23 H34 Cl N9 O3

PAGE 1-A



PAGE 1-B

CM 2

CRN 75-75-2
CMF C H4 O3 S

RN 876131-08-7 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[4-[4-(1-piperazinylcarbonyl)phenyl]butyl]amino]methyl]-,dimethanesulfonate (9CI) (CA INDEX NAME)

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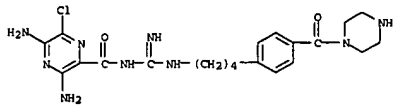
CRN 876130-98-2
CMF C21 H28 Cl N9 O2

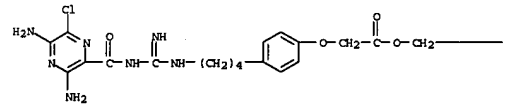


CM 2

CRN 75-75-2
CMF C H4 O3 S

RN 876131-09-8 CAPLUS
CN Acetic acid, [4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]imino methyl]amino]butyl]phenoxy]-, 4-piperidinylmethyl ester, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A

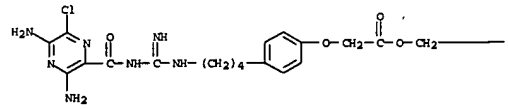


●2 HCl

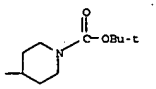
PAGE 1-B

IT 876131-39-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of soluble amide and ester pyrazinoylguanidines as sodium channel
blockers)
RN 876131-39-4 CAPLUS
CN 1-Piperidinecarboxylic acid, 4-[[[[4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenoxy]acetyl]oxy]methyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 1-B



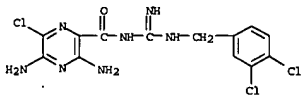
L6 ANSWER 7 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:588886 CAPLUS
DOCUMENT NUMBER: 143:91034
TITLE: Compositions and methods for treating vascular conditions
INVENTOR(S): Dear, Anthony E.; Widdop, Robert; Gaspari, Tracey; Vinh, Antony; Martin, David; Dousha, Lovisha F.
PATENT ASSIGNEE(S): Monash University, Australia
SOURCE: PCT Int. Appl., 94 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005061448	A1	20050707	WO 2004-AU1829	20041224
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT,				

RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

		US 2004-920626	A 20040818
		US 2003-495712P	P 20030818
		US 2003-495720P	P 20030818
		US 2003-495725P	P 20030818
		US 2004-920410	A3 20040818
		WO 2004-US26963	W 20040819

PRIORITY APPLN. INFO.: AU 2003-907185 A 20031224
OTHER SOURCE(S): MARPAT 143:91034
AB The present invention provides methods for treating vascular diseases such an aneurysm (particularly abdominal aortic aneurysm) and neointimal hyperplasia. The methods include use of known compds. such as amiloride and oxamflatin, and also novel hydroxamic acid derivs.
IT 1166-01-4, Dichlorobenzamil
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. for treating vascular conditions)
RN 1166-01-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 8 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:346797 CAPLUS
DOCUMENT NUMBER: 142:411366
TITLE: Preparation of pyridazinylcarbonyl-substitutedureas used for reducing risk of infection from pathogens
INVENTOR(S): Johnson, Michael R.; Hopkins, Samuel E.
PATENT ASSIGNEE(S): Parion Sciences, Inc., USA
SOURCE: PCT Int. Appl., 218 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005034847	A2	20050421	WO 2004-US26963	20040819
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RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2005090505	A1	20050428	US 2004-920626	20040818
AU 2004279329	A1	20050421	AU 2004-279329	20040819
CA 2533886	A1	20050421	CA 2004-2533886	20040819
EP 1656096	A2	20060517	EP 2004-809587	20040819
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US 2006205738	A1	20060914	US 2005-211707	20050826

PRIORITY APPLN. INFO.: US 2003-496481P P 20030820

OTHER SOURCE(S): MARPAT 142:411366
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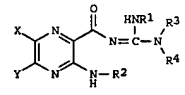

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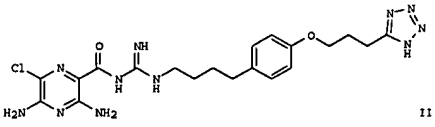
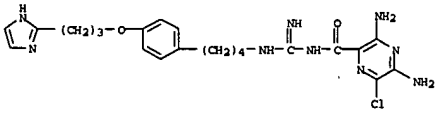


II

AB Title compds. I [X = H, halo, CF3, etc.; Y = H, OH, SH, etc.; R1 = H, alkyl; R2 = alkoxy, etc.; R3-4 = H, alkyl, OH, alkyl, Ph, etc.] are prepared For instance, II is prepared in 4 steps from [4-(4-hydroxyphenyl)butyl]carbamic acid benzyl ester (preparation given), 4-bromobutyronitrile and 1-(3,5-diamino-6-chloropyrazine-2-carbonyl)-2-methylisothiourea-HI. II has EC50 = 25 nM in a sodium channel blocker assay. I are useful for prophylactic treatment to one or more members of a population at risk of exposure to or already exposed to one or more airborne pathogens, either from natural sources or from intentional release of pathogens into the environment.
IT 847236-91-3P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of pyridazinylcarbonyl-substitutedureas used for reducing risk of infection from pathogens)
RN 847236-91-3 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[3-(1H-imidazol-2-yl)propoxy]phenyl]butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



IT 847200-78-6P 847200-85-5P 847200-86-6P

847200-87-7P 847200-88-8P 847200-89-9P
847200-90-2P 847200-91-3P 847200-94-6P
847236-78-6P 847236-85-5P 847236-86-6P
847236-87-7P 847236-88-8P 847236-89-9P
847236-90-2P 847236-92-4P 847236-93-5P
847236-94-6P 847236-95-7P 847236-96-8P
847236-98-0P 847236-99-1P 847237-00-7P
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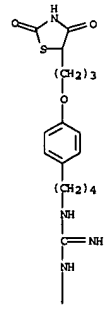
847237-04-1P 847237-05-2P 847354-46-5P
847354-47-6P 850537-03-0P 850537-04-1P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of pyridazinylcarbonyl-substitutedureas used for reducing risk of infection from pathogens)

RN 847200-78-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[3-(2,4-dioxo-5-thiazolidinyl)propoxy]phenyl]butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)

PAGE 1-A



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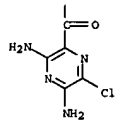
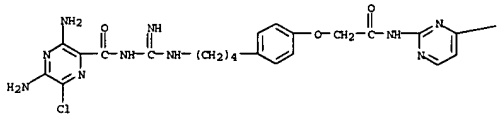


RN 847200-85-5 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[3-

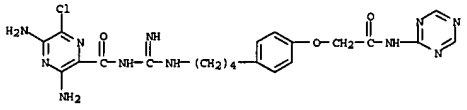
(9CI) (CA INDEX NAME)

PAGE 1-A



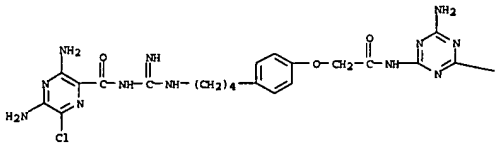
PAGE 1-B

RN 847200-88-8 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[4-[4-[2-oxo-2-(1,3,5-triazin-2-ylamino)ethoxy]phenyl]butyl]amino]methyl]-(9CI) (CA INDEX NAME)

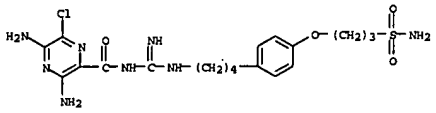


RN 847200-89-9 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[2-[(4,6-diamino-1,3,5-triazin-2-yl)amino]-2-oxoethoxy]phenyl]butyl]amino]iminomethyl] (9CI) (CA INDEX NAME)

PAGE 1-A

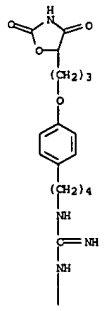


(aminosulfonyl)propoxy]phenyl]butyl]amino]iminomethyl]-6-chloro (9CI) (CA INDEX NAME)



RN 847200-86-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[3-(2,4-dioxo-5-oxazolidinyl)propoxy]phenyl]butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)

PAGE 1-A



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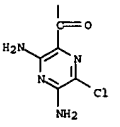
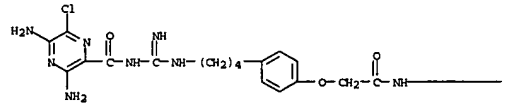


RN 847200-87-7 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[2-[(4-amino-2-pyrimidinyl)amino]-2-oxoethoxy]phenyl]butyl]amino]iminomethyl]-6-chloro-

PAGE 1-B

RN 847200-90-2 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[2-[(6-amino-1H-purin-2-yl)amino]-2-oxoethoxy]phenyl]butyl]amino]iminomethyl]-6-chloro (9CI) (CA INDEX NAME)

PAGE 1-A



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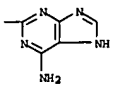
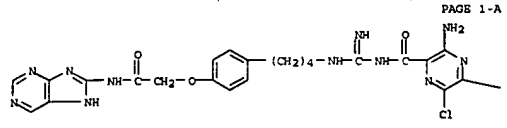


RN 847200-91-3 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[4-[4-[2-oxo-2-(1H-purin-8-ylamino)ethoxy]phenyl]butyl]amino]methyl]-(9CI) (CA INDEX NAME)

PAGE 1-A

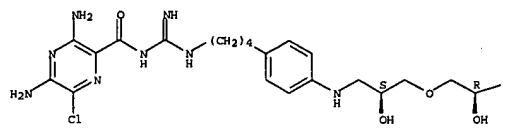


PAGE 1-B

RN 847200-94-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[[(2S)-3-[(2R)-2,3-dihydroxypropoxy]-2-hydroxypropyl]amino]phenyl]butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)

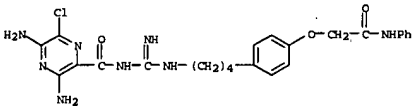
Absolute stereochemistry.

PAGE 1-A

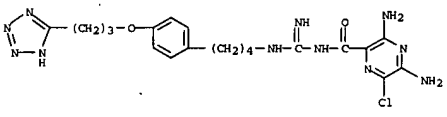


PAGE 1-B

RN 847236-78-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[4-[4-[2-oxo-2-(phenylamino)ethoxy]phenyl]butyl]amino]methyl]-(9CI) (CA INDEX NAME)

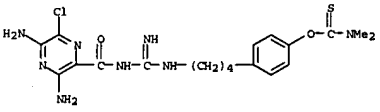


RN 847236-85-5 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[2-(1H-imidazol-2-ylamino)-2-oxoethoxy]phenyl]butyl]amino]iminomethyl]-,dihydrochloride (9CI) (CA INDEX NAME)



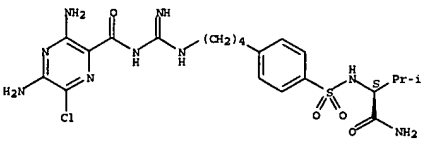
● HCl

RN 847236-89-9 CAPLUS
CN Carbamothioic acid, dimethyl-, O-[4-[4-[[[[(3,5-diamino-6-chloropyrazinyl]carbonyl]amino]iminomethyl]amino]butyl]phenyl ester (9CI) (CA INDEX NAME)



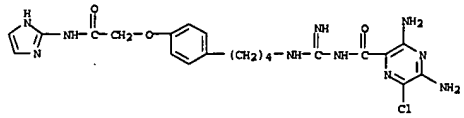
RN 847236-90-2 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[[[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]sulfonyl]phenyl]butyl]amino]iminomethyl]-6-chloro-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



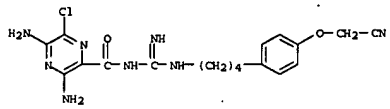
● HCl

RN 847236-92-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[2-[bis(2-hydroxyethyl)amino]-2-oxoethoxy]phenyl]butyl]amino]iminomethyl]-6-chloro-(9CI) (CA INDEX NAME)



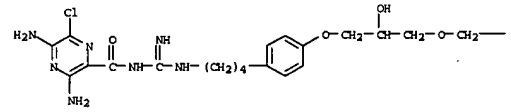
● 2 HCl

RN 847236-86-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-(cyanomethoxy)phenyl]butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)

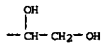


RN 847236-87-7 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[3-(2,3-dihydroxypropoxy)-2-hydroxypropoxy]phenyl]butyl]amino]iminomethyl] (9CI) (CA INDEX NAME)

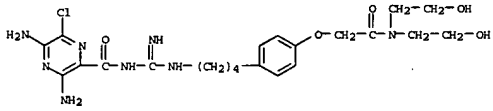
PAGE 1-A



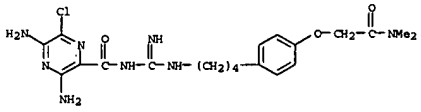
PAGE 1-B



RN 847236-88-8 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[4-[4-[3-(1H-tetrazol-5-yl)propoxy]phenyl]butyl]amino]methyl]-,monohydrochloride (9CI) (CA INDEX NAME)

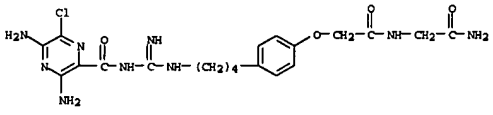


RN 847236-93-5 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[2-(dimethylamino)-2-oxoethoxy]phenyl]butyl]amino]iminomethyl]-,monohydrochloride (9CI) (CA INDEX NAME)

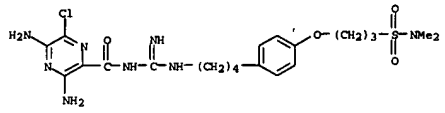


● HCl

RN 847236-94-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[2-[(2-amino-2-oxoethyl)amino]-2-oxoethoxy]phenyl]butyl]amino]iminomethyl]-6-chloro-(9CI) (CA INDEX NAME)

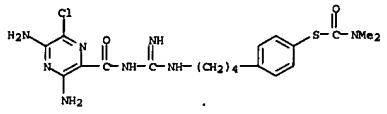


RN 847236-95-7 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[3-[(dimethylamino)sulfonyl]propoxy]phenyl]butyl]amino]iminomethyl]-, monohydrochloride (9CI) (CA INDEX NAME)

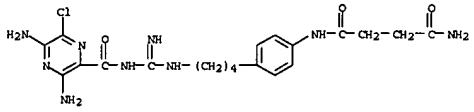


● HCl

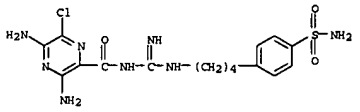
RN 847236-96-8 CAPLUS
CN Carbamothioic acid, dimethyl-, S-[4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenyl] ester (9CI) (CA INDEX NAME)



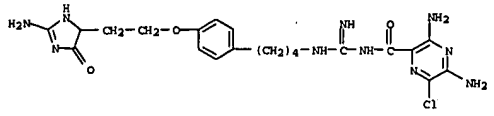
RN 847236-98-0 CAPLUS
CN Butanediamide, N-[4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenyl]- (9CI) (CA INDEX NAME)



RN 847236-99-1 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-(aminosulfonyl)phenyl]butyl]amino]iminomethyl]-6-chloro- (9CI) (CA INDEX NAME)

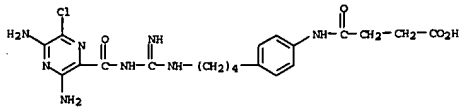


RN 847237-00-7 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[2-(2-amino-4,5-dihydro-5-oxo-1H-imidazol-4-yl)ethoxy]phenyl]butyl]amino]iminomethyl]-6-chloro-, dihydrochloride (9CI) (CA INDEX NAME)



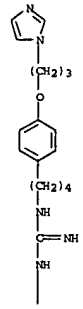
●2 HCl

RN 847237-01-8 CAPLUS
CN Butanoic acid, 4-[[4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenyl]amino]-4-oxo-(9CI) (CA INDEX NAME)

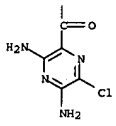


RN 847237-02-9 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[3-(1H-imidazol-1-yl)propoxy]phenyl]butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)

PAGE 1-A

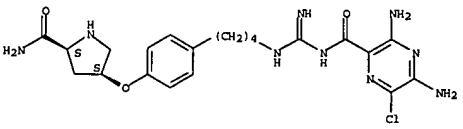


PAGE 2-A



RN 847237-03-0 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[[(3S,5S)-5-(aminocarbonyl)-3-pyrrolidinyl]oxy]phenyl]butyl]amino]iminomethyl]-6-chloro-, dihydrochloride (9CI) (CA INDEX NAME)

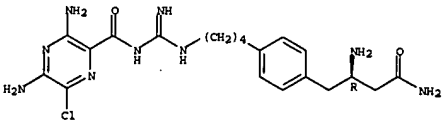
Absolute stereochemistry. Rotation (-).



●2 HCl

RN 847237-04-1 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[(2R)-2,4-diamino-4-oxobutyl]phenyl]butyl]amino]iminomethyl]-,dihydrochloride (9CI) (CA INDEX NAME)

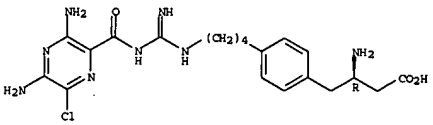
Absolute stereochemistry. Rotation (+).



●2 HCl

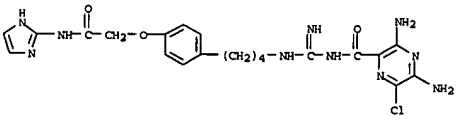
RN 847237-05-2 CAPLUS
CN Benzenebutanoic acid, β-amino-4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]-,dihydrochloride, (βR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

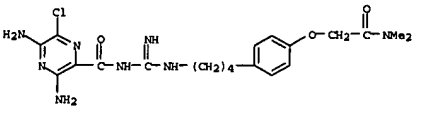


●2 HCl

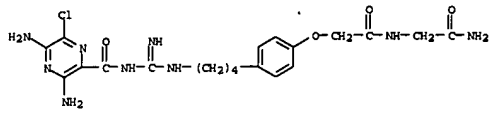
RN 847354-46-5 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[2-(1H-imidazol-2-ylamino)-2-oxoethoxy]phenyl]butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



RN 847354-47-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[2-(dimethylamino)-2-oxoethoxy]phenyl]butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)

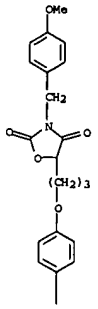


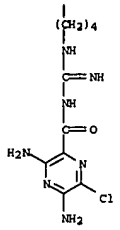
RN 850537-03-0 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[2-[(2-amino-2-oxoethyl)amino]-2-oxoethoxy]phenyl]butyl]amino]iminomethyl]-6-chloro-,hydrochloride (9CI) (CA INDEX NAME)



●x HCl

RN 850537-04-1 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[4-[4-[3-[[(4-methoxyphenyl)methyl]-2,4-dioxo-5-oxazolidinyl]propoxy]phenyl]butyl]amino]methyl]-, monohydrochloride (9CI) (CA INDEX NAME)





● HCl

L6 ANSWER 9 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:325702 CAPLUS
DOCUMENT NUMBER: 142:367646
TITLE: Methods using sodium channel blockers for reducing risk of infection from pathogens
INVENTOR(S): Johnson, Michael R.; Hopkins, Samuel E.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 52 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005080093	A1	20050414	US 2004-920484	20040818
AU 2004287352	A1	20050519	AU 2004-287352	20040819
CA 2534069	A1	20050519	CA 2004-2534069	20040819
WO 2005044180	A2	20050519	WO 2004-US26778	20040819
WO 2005044180	A3	20051006		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

EP 1656022	A2	20060517	EP 2004-816810	20040819

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR

PRIORITY APPLN. INFO.:	US 2003-496482P	P	20030820
	US 2004-920484	A	20040818
	WO 2004-US26778	W	20040819

OTHER SOURCE(S): MARPAT 142:367646

AB Prophylactic treatment methods are provided for protection of individuals and/or populations against infection from airborne pathogens. In particular, prophylactic treatment methods are provided comprising administering a sodium channel blocker or pharmaceutically acceptable salt thereof to one or more members of a population at risk of exposure to or already exposed to one or more airborne pathogens, either from natural sources or from intentional release of pathogens into the environment.

IT 583825-14-3 583825-15-4 583825-16-5
583825-18-7 583825-23-4 583825-25-6
587879-24-1 587879-25-2 587879-26-3
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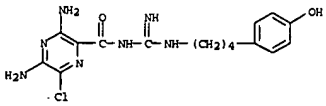
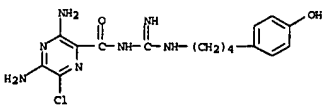
742102-05-2 849588-69-8 849588-70-1
849588-71-2 849588-72-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(sodium channel blockers for reducing risk of infection from pathogens)

RN 583825-14-3 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-(4-hydroxyphenyl)butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)

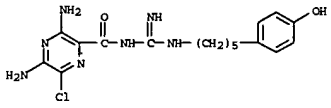


RN 583825-15-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-(4-hydroxyphenyl)butyl]amino]iminomethyl]-,monohydrochloride (9CI) (CA INDEX NAME)

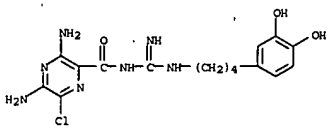


● HCl

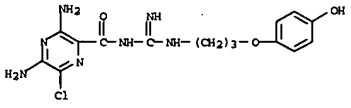
RN 583825-16-5 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[5-(4-hydroxyphenyl)pentyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



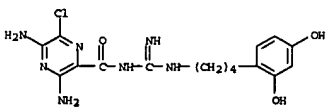
RN 583825-18-7 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-(3,4-dihydroxyphenyl)butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



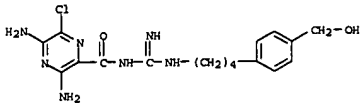
RN 583825-23-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[3-(4-hydroxyphenoxy)propyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



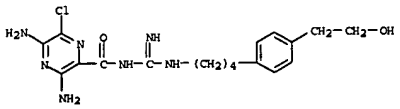
RN 583825-25-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-(2,4-dihydroxyphenyl)butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



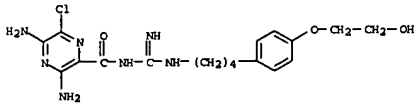
RN 587879-24-1 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-(hydroxymethyl)phenyl]butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



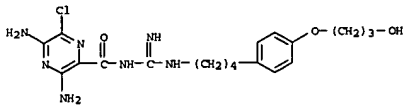
RN 587879-25-2 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-(2-hydroxyethyl)phenyl]butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



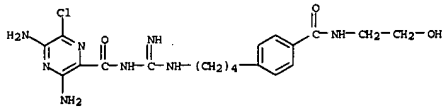
RN 587879-26-3 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-(2-hydroxyethoxy)phenyl]butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



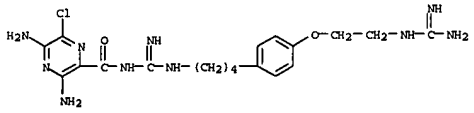
RN 587879-28-5 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-(3-hydroxypropoxy)phenyl]butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



RN 587879-29-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-(4-aminophenyl)butyl]amino]iminomethyl]-6-chloro- (9CI) (CA INDEX NAME)

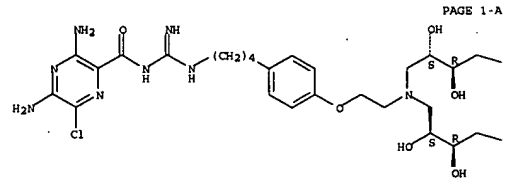


RN 587879-46-7 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[2-[(aminoiminomethyl)amino]ethoxy]phenyl]butyl]amino]iminomethyl]-6-chloro-(9CI) (CA INDEX NAME)



RN 587879-50-3 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[2-[bis[(2S,3R)-2,3,4-trihydroxybutyl]amino]ethoxy]phenyl]butyl]amino]iminomethyl]-6-chloro-(9CI) (CA INDEX NAME)

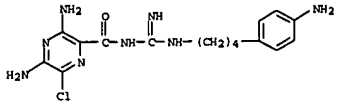
Absolute stereochemistry. Rotation (-).



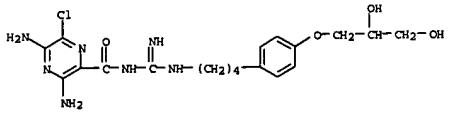
PAGE 1-A

PAGE 1-B

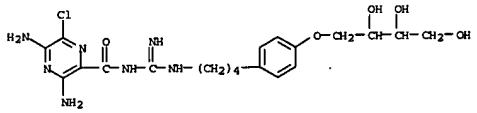
RN 587879-57-0 CAPLUS



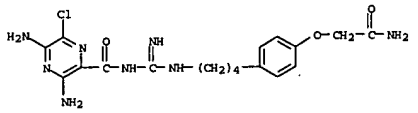
RN 587879-32-1 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-(2,3-dihydroxypropoxy)phenyl]butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



RN 587879-34-3 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[4-[4-(2,3,4-trihydroxybutoxy)phenyl]butyl]amino]methyl]-(9CI) (CA INDEX NAME)

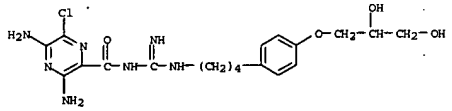


RN 587879-43-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-(2-amino-2-oxoethoxy)phenyl]butyl]amino]iminomethyl]-6-chloro-(9CI) (CA INDEX NAME)



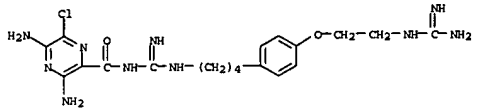
RN 587879-44-5 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[[(2-hydroxyethyl)amino]carbonyl]phenyl]butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)

CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-(2,3-dihydroxypropoxy)phenyl]butyl]amino]iminomethyl]-,monohydrochloride (9CI) (CA INDEX NAME)



● HCl

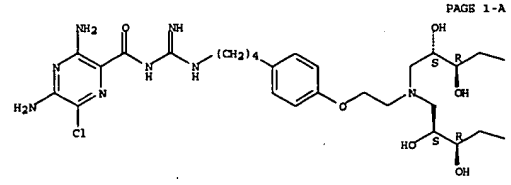
RN 587879-80-9 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[2-[(aminoiminomethyl)amino]ethoxy]phenyl]butyl]amino]iminomethyl]-6-chloro-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

RN 587879-81-0 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[2-[bis[(2S,3R)-2,3,4-trihydroxybutyl]amino]ethoxy]phenyl]butyl]amino]iminomethyl]-6-chloro-, dihydrochloride (9CI) (CA INDEX NAME)

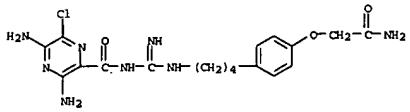
Absolute stereochemistry. Rotation (-).



PAGE 1-A

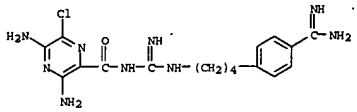
●2 HCl

RN 587879-86-5 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-(2-amino-2-oxoethoxy)phenyl]butyl]amino]iminomethyl]-6-chloro-,monohydrochloride (9CI) (CA INDEX NAME)

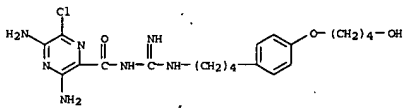


● HCl

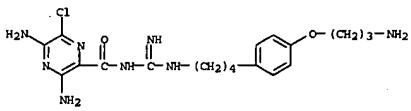
RN 587879-87-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-(amino[[4-[4-(aminoiminomethyl)phenyl]butyl]amino]methylene]-6-chloro-(9CI) (CA INDEX NAME)



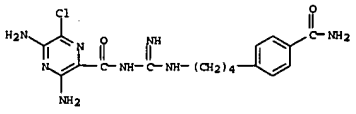
RN 587879-88-7 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-(4-hydroxybutyl)phenyl]butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



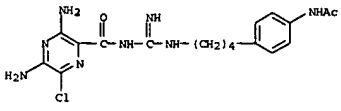
RN 587879-93-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-(3-aminopropoxy)phenyl]butyl]amino]iminomethyl]-6-chloro-(9CI) (CA INDEX NAME)



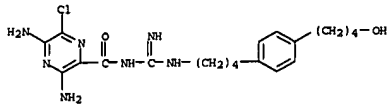
RN 587879-94-5 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-(aminocarbonyl)phenyl]butyl]amino]iminomethyl]-6-chloro- (9CI) (CA INDEX NAME)



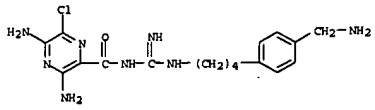
RN 587879-95-6 CAPLUS
CN Pyrazinecarboxamide, N-[[[4-[4-(acetylamino)phenyl]butyl]amino]iminomethyl]-3,5-diamino-6-chloro- (9CI) (CA INDEX NAME)



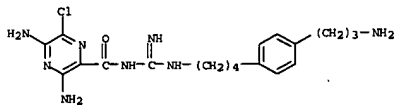
RN 587879-96-7 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[4-[4-[(methylsulfonyl)amino]phenyl]butyl]amino]methyl]-(9CI) (CA INDEX NAME)



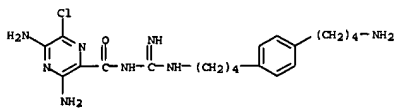
RN 587879-89-8 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-(aminomethyl)phenyl]butyl]amino]iminomethyl]-6-chloro- (9CI) (CA INDEX NAME)



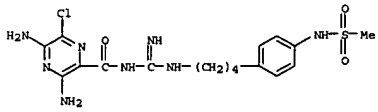
RN 587879-90-1 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-(3-aminopropyl)phenyl]butyl]amino]iminomethyl]-6-chloro-(9CI) (CA INDEX NAME)



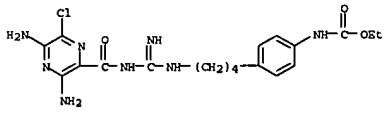
RN 587879-91-2 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-(4-aminobutyl)phenyl]butyl]amino]iminomethyl]-6-chloro-(9CI) (CA INDEX NAME)



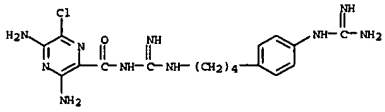
RN 587879-92-3 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-(4-hydroxybutoxy)phenyl]butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



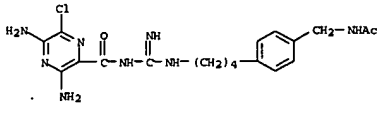
RN 587879-97-8 CAPLUS
CN Carbamic acid, [4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenyl]-, ethyl ester (9CI) (CA INDEX NAME)



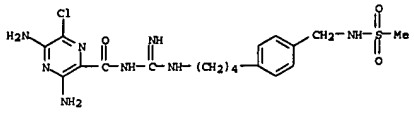
RN 587879-98-9 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[(aminoiminomethyl)amino]phenyl]butyl]amino]iminomethyl]-6-chloro-(9CI) (CA INDEX NAME)



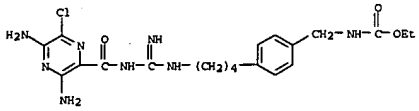
RN 587879-99-0 CAPLUS
CN Pyrazinecarboxamide, N-[[[4-[4-[(acetylamino)methyl]phenyl]butyl]amino]iminomethyl]-3,5-diamino-6-chloro- (9CI) (CA INDEX NAME)



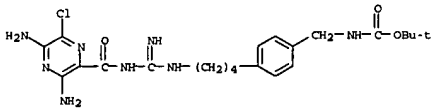
RN 587880-00-0 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[4-[4-[[(methylsulfonyl)amino]methyl]phenyl]butyl]amino]methyl]-(9CI) (CA INDEX NAME)



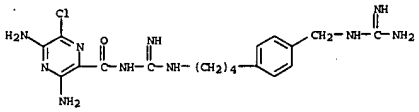
RN 587880-01-1 CAPLUS
CN Carbamic acid, [[4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenyl]methyl]-,ethyl ester (9CI) (CA INDEX NAME)



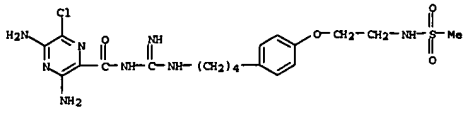
RN 587880-02-2 CAPLUS
CN Carbamic acid, [[4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenyl]methyl]-,1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



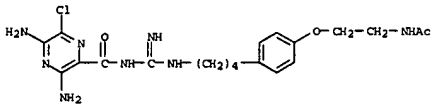
RN 587880-03-3 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[[(aminoiminomethyl)amino]methyl]phenyl]butyl]amino]iminomethyl]-6-chloro-(9CI) (CA INDEX NAME)



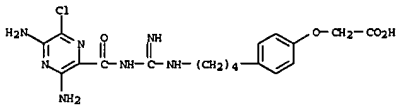
RN 587880-04-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[4-[4-[2-[(methylsulfonyl)amino]ethoxy]phenyl]butyl]amino]methyl]-(9CI) (CA INDEX NAME)



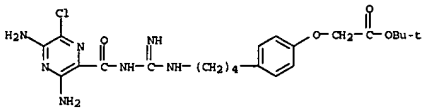
RN 587880-05-5 CAPLUS
CN Pyrazinecarboxamide, N-[[[4-[4-[2-(acetylamino)ethoxy]phenyl]butyl]amino]iminomethyl]-3,5-diamino-6-chloro-(9CI) (CA INDEX NAME)



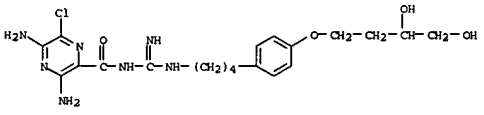
RN 587880-06-6 CAPLUS
CN Acetic acid, [4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenoxy]-(9CI) (CA INDEX NAME)



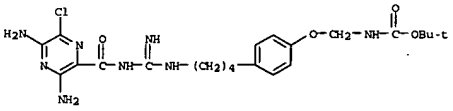
RN 587880-07-7 CAPLUS
CN Acetic acid, [4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenoxy]-,1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



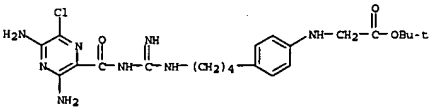
RN 587880-08-8 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-(3,4-dihydroxybutoxy)phenyl]butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



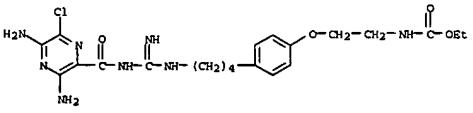
RN 587880-10-2 CAPLUS
CN Carbamic acid, [[4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenoxy]methyl]-,1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



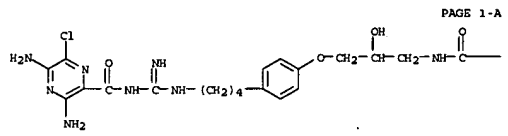
RN 587880-12-4 CAPLUS
CN Glycine, N-[4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



RN 587880-13-5 CAPLUS
CN Carbamic acid, [2-[4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenoxy]ethyl]-,ethyl ester (9CI) (CA INDEX NAME)



RN 587880-14-6 CAPLUS
CN Carbamic acid, [3-[4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenoxy]-2-hydroxypropyl]-,1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

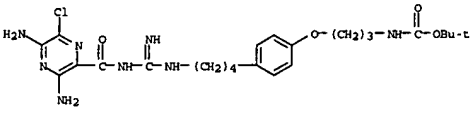


PAGE 1-A

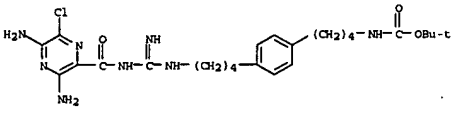
PAGE 1-B

—OBu-t

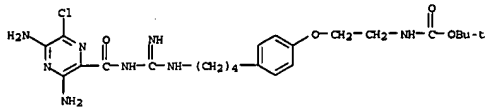
RN 587880-15-7 CAPLUS
CN Carbamic acid, [3-[4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenoxy]propyl]-,1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



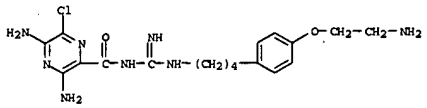
RN 587880-16-8 CAPLUS
CN Carbamic acid, [4-[4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenyl]butyl]-,1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



RN 587880-56-6 CAPLUS
CN Carbamic acid, [2-[4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenoxy]ethyl]-,1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

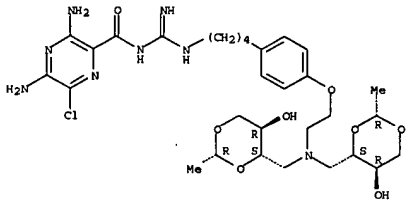


RN 587880-57-7 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-(2-aminoethoxy)phenyl]butyl]amino]iminomethyl]-6-chloro-(9CI) (CA INDEX NAME)



RN 587880-62-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[2-[bis[[(2R,4S,5R)-5-hydroxy-2-methyl-1,3-dioxan-4-yl]methyl]amino]ethoxy]phenyl]butyl]amino]iminomethyl]-6-chloro- (9CI) (CA INDEX NAME)

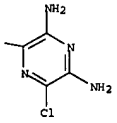
Absolute stereochemistry. Rotation (-).



RN 587880-69-1 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[2-[[[(2R,4S,5R)-5-hydroxy-2-methyl-1,3-dioxan-4-yl]methyl]amino]ethoxy]phenyl]butyl]amino]iminomethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

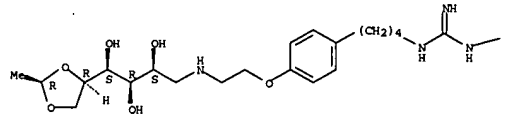
PAGE 1-B



RN 742102-03-0 CAPLUS
CN D-Glucitol, 1-[[2-[4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenoxy]ethyl]amino]-1-deoxy-5,6-O-(1R)-ethylidene- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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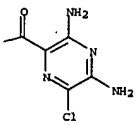
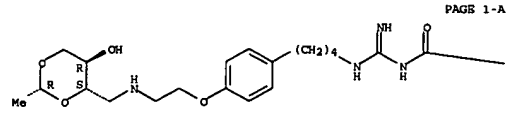


RN 742102-04-1 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[2-[bis[[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl]amino]ethoxy]phenyl]butyl]amino]iminomethyl]-6-chloro- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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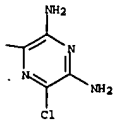
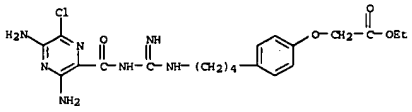


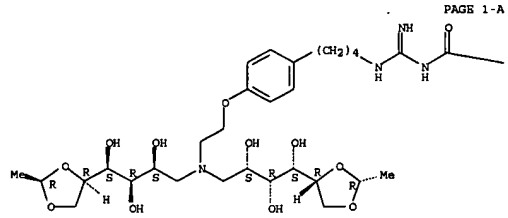
RN 587880-76-0 CAPLUS
CN Acetic acid, [4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenoxy]-, ethyl ester (9CI) (CA INDEX NAME)

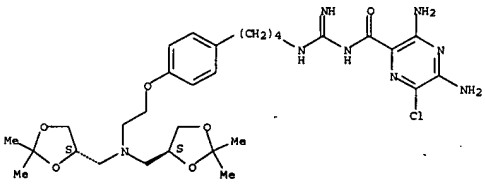


RN 742102-02-9 CAPLUS
CN D-Glucitol, 1,1'-[[2-[4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenoxy]ethyl]imino]bis[1-deoxy-5,6-O-(1R)-ethylidene-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

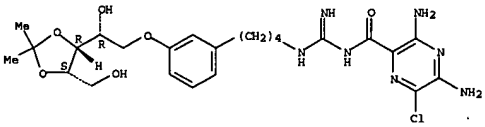
PAGE 1-A





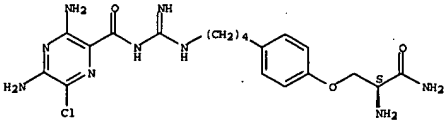
RN 742102-05-2 CAPLUS
CN D-Ribitol, 5-O-[3-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenyl]-2,3-O-(1-methylethylidene)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

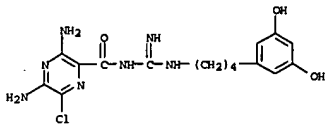


RN 849588-69-8 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[(2S)-2,3-diamino-3-oxopropoxy]phenyl]butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)

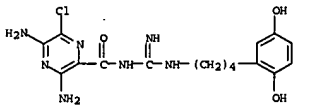
Absolute stereochemistry.



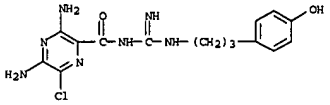
RN 849588-70-1 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-(3,5-dihydroxyphenyl)butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



RN 849588-71-2 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-(2,5-dihydroxyphenyl)butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



RN 849588-72-3 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[3-(4-hydroxyphenyl)propyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



L6 ANSWER 10 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:177896 CAPLUS
DOCUMENT NUMBER: 142:280225
TITLE: Preparation of capped aminopyrazinoylguanidines as sodium channel blockers
INVENTOR(S): Johnson, Michael R.; Molino, Bruce F.; Zhang, Jianzhong; Sargent, Bruce J.
PATENT ASSIGNEE(S): Parion Sciences, Inc., USA
SOURCE: PCT Int. Appl., 100 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005018644	A1	20050303	WO 2004-US26885	20040818
WO 2005018644	B1	20050512		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
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AU 2004266704	A1	20050303	AU 2004-266704	20040818
CA 2534682	A1	20050303	CA 2004-2534682	20040818
US 2005080091	A1	20050414	US 2004-920410	20040818
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EP 1663235	A1	20060607	EP 2004-781545	20040818

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JP 2007502830	T	20070215	JP 2006-524028	20040818
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PRIORITY APPLN. INFO.:			US 2003-495725P	P 20030818
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			WO 2004-US26885	W 20040818

OTHER SOURCE(S): CASREACT 142:280225; MARPAT 142:280225
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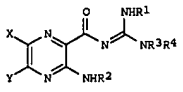


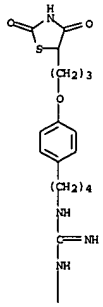
I

AB Title compds. [I; X = H, halo, CF3, alkyl, (substituted) Ph, etc.; Y = H, OH, SH, alkoxy, alkylthio, halo, alkyl, (substituted) aryl, etc.; R1 = H, alkyl; R2 = R7, (CH2)mOR8, (CH2)mNR7R10, (CH2CH2O)mR8, etc.; m = 1-7; R3, R4 = H, alkyl, hydroxyalkyl, Ph, phenylalkyl, naphthylalkyl, pyridylalkyl, etc.; R7 = H, alkyl, (substituted) Ph, etc.; R8 = H, alkyl, 2-tetrahydropyranyl, glucuronide, etc.; R10 = H, SO2Me, COR13, CO2R13, etc.; R13 = H, R7, R10, etc.; with provisos], were prepared Thus, [4-(4-hydroxyphenyl)butyl]carbamicacid benzyl ester in EtOH at 70° was treated with oxiranylmethanol over 4 h to give 4.6% [4-[4-[3-(2,3-dihydroxypropoxy)-2-hydroxypropoxy]phenyl]butyl]carbamic acid benzyl ester. This was hydrogenolyzed in EtOH over Pd/C to give 51% 3-[3-[4-(4-aminobutyl)phenoxy]-2-hydroxypropoxy]propane-1,2-diol. The latter was stirred with Et3N and 1-(3,5-diamino-6-chloropyrazine-2-carbonyl)-2-methylisothioureahydroiodide in EtOH at 65° to give 36% N-(3,5-diamino-6-chloropyrazine-2-carbonyl)-N'-[4-[4-[3-(2,3-dihydroxypropoxy)-2-hydroxypropoxy]phenyl]butyl]guanidin(PSA 15143). The latter showed Na channel blocking activity with EC50 = 7 nM.

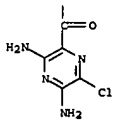
IT 847200-78-6P 847200-80-0P 847200-82-2P
847200-84-4P 847200-85-5P 847200-86-6P
847200-87-7P 847200-88-8P 847200-89-9P
847200-90-2P 847200-91-3P 847200-92-4P
847200-93-5P 847200-94-6P 847236-78-6I, PSA
17482 847236-85-5I, PSA 16437 847236-86-6I, PSA 16208
847236-87-7I, PSA 15143
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(claimed compound; preparation of aminopyrazinoylguanidines as sodium channel blockers)

RN 847200-78-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[3-(2,4-dioxo-5-thiazolidinyl)propoxy]phenyl]butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)

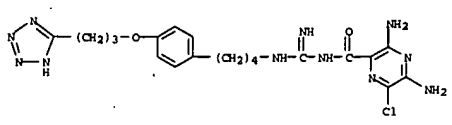
PAGE 1-A



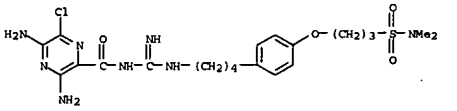
PAGE 2-A



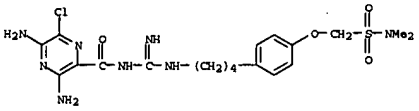
RN 847200-80-0 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[4-[4-[3-(1H-tetrazol-5-yl)propoxy]phenyl]butyl]amino]methyl]-(9CI) (CA INDEX NAME)



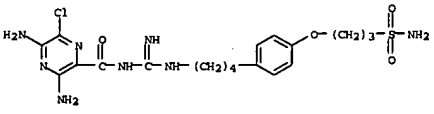
RN 847200-82-2 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[4-[3-[(dimethylamino)sulfonyl]propoxy]phenyl]butyl]amino]iminomethyl] (9CI) (CA INDEX NAME)



RN 847200-84-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[[(dimethylamino)sulfonyl]methoxy]phenyl]butyl]amino]iminomethyl] (9CI) (CA INDEX NAME)

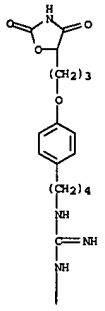


RN 847200-85-5 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[3-(aminosulfonyl)propoxy]phenyl]butyl]amino]iminomethyl]-6-chloro (9CI) (CA INDEX NAME)

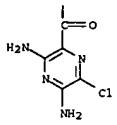


RN 847200-86-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[3-(2,4-dioxo-5-oxazolidinyl)propoxy]phenyl]butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)

PAGE 1-A

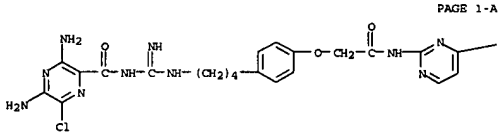


PAGE 2-A

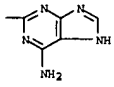


RN 847200-87-7 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[2-[(4-amino-2-pyrimidinyl)amino]-2-oxoethoxy]phenyl]butyl]amino]iminomethyl]-6-chloro- (9CI) (CA INDEX NAME)

PAGE 1-A

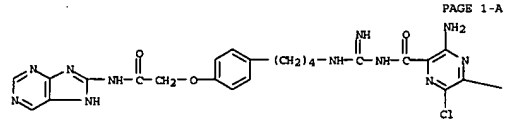


PAGE 1-B



RN 847200-91-3 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[4-[4-[2-oxo-2-(1H-purin-8-ylamino)ethoxy]phenyl]butyl]amino]methyl]-(9CI) (CA INDEX NAME)

PAGE 1-A

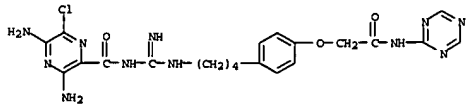


PAGE 1-B

RN 847200-92-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[3-(1H-imidazol-2-yl)propoxy]phenyl]butyl]amino]iminomethyl]-,monohydrochloride (9CI) (CA INDEX NAME)

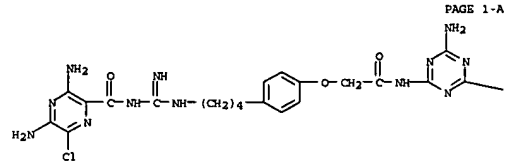
PAGE 1-B

RN 847200-88-8 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[4-[4-[2-oxo-2-(1,3,5-triazin-2-ylamino)ethoxy]phenyl]butyl]amino]methyl]-(9CI) (CA INDEX NAME)



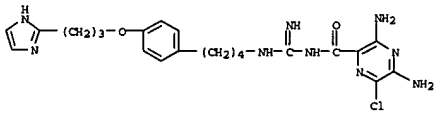
RN 847200-89-9 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[2-[(4,6-diamino-1,3,5-triazin-2-yl)amino]-2-oxoethoxy]phenyl]butyl]amino]iminomethyl] (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 1-B

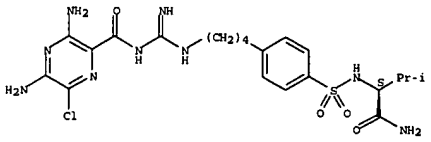
RN 847200-90-2 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[2-[(6-amino-1H-purin-2-yl)amino]-2-oxoethoxy]phenyl]butyl]amino]iminomethyl]-6-chloro (9CI) (CA INDEX NAME)



● HCl

RN 847200-93-5 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[[[[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]sulfonyl]phenyl]butyl]amino]iminomethyl]-6-chloro- (9CI) (CA INDEX NAME)

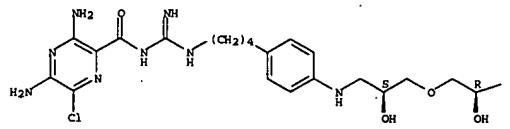
Absolute stereochemistry. Rotation (+).



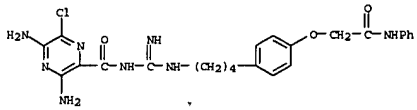
RN 847200-94-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[[(2S)-3-[(2R)-2,3-dihydroxypropoxy]-2-hydroxypropyl]amino]phenyl]butyl]amino]iminomethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

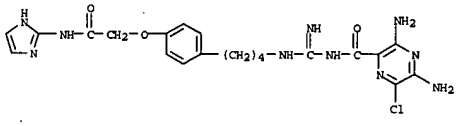
PAGE 1-A



RN 847236-78-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[4-[4-[2-oxo-2-(phenylamino)ethoxy]phenyl]butyl]amino]methyl]-(9CI) (CA INDEX NAME)

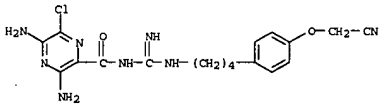


RN 847236-85-5 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[2-(1H-imidazol-2-ylamino)-2-oxoethoxy]phenyl]butyl]amino]iminomethyl]-,dihydrochloride (9CI) (CA INDEX NAME)

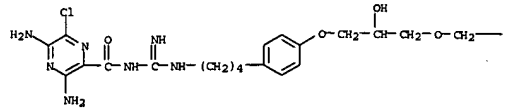


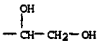
●2 HCl

RN 847236-86-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-(cyanomethoxy)phenyl]butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



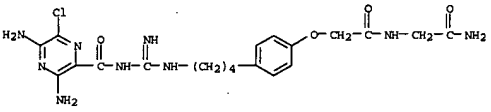
RN 847236-87-7 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[3-(2,3-dihydroxypropoxy)-2-hydroxypropoxy]phenyl]butyl]amino]iminomethyl] (9CI) (CA INDEX NAME)





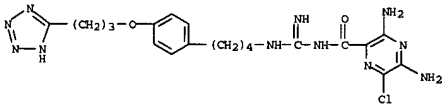
IT 847200-95-7P 847236-88-8P, PSA 17926
847236-89-9P, PSA 17846 847236-90-2P, PSA 19008
847236-91-3P, PSA 23022 847236-92-4P, PSA 16826
847236-93-5P, PSA 16313 847236-94-6P, PSA 16314
847236-95-7P, PSA 17927 847236-96-8P, PSA 18211
847236-97-9P, PSA 18212 847236-98-0P, PSA 18229
847236-99-1P, PSA 18361 847237-00-7P, PSA 18592
847237-01-8P, PSA 18593 847237-02-9P, PSA 19007
847237-03-0P, PSA 19912 847237-04-1P, PSA 24406
847237-05-2P, PSA 24407
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of aminopyrazinoylguanidines as sodium channel blockers)

RN 847200-95-7 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[2-[(2-amino-2-oxoethyl)amino]-2-oxoethoxy]phenyl]butyl]amino]iminomethyl]-6-chloro-,monohydrochloride (9CI) (CA INDEX NAME)



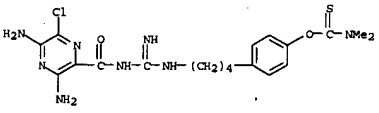
● HCl

RN 847236-88-8 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[4-[4-[3-(1H-tetrazol-5-yl)propoxy]phenyl]butyl]amino]methyl]-,monohydrochloride (9CI) (CA INDEX NAME)



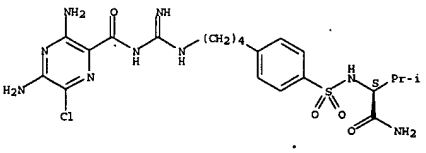
● HCl

RN 847236-89-9 CAPLUS
CN Carbamothioic acid, dimethyl-, O-[4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenyl] ester (9CI) (CA INDEX NAME)



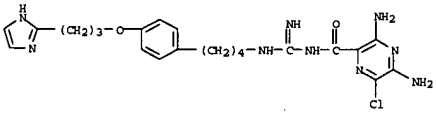
RN 847236-90-2 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[[[(1S)-1-(aminocarbonyl)-2-methylpropyl]amino]sulfonyl]phenyl]butyl]amino]iminomethyl]-6-chloro-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

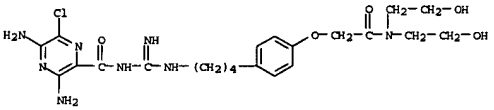


● HCl

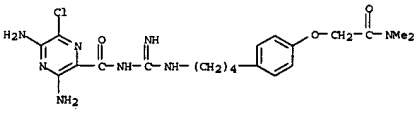
RN 847236-91-3 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[3-(1H-imidazol-2-yl)propoxy]phenyl]butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



RN 847236-92-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[2-[bis(2-hydroxyethyl)amino]-2-oxoethoxy]phenyl]butyl]amino]iminomethyl]-6-chloro-(9CI) (CA INDEX NAME)

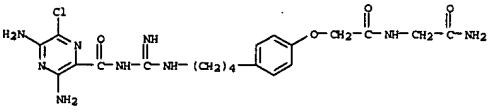


RN 847236-93-5 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[2-(dimethylamino)-2-oxoethoxy]phenyl]butyl]amino]iminomethyl]-,monohydrochloride (9CI) (CA INDEX NAME)



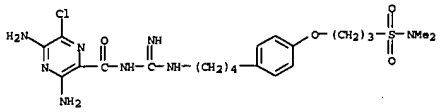
● HCl

RN 847236-94-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[2-[(2-amino-2-oxoethyl)amino]-2-oxoethoxy]phenyl]butyl]amino]iminomethyl]-6-chloro-(9CI) (CA INDEX NAME)



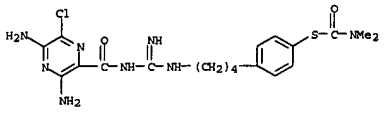
RN 847236-95-7 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[3-[(dimethylamino)sulfonyl]propoxy]phenyl]butyl]amino]iminomethyl]-,

monohydrochloride (9CI) (CA INDEX NAME)

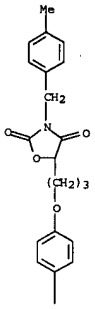


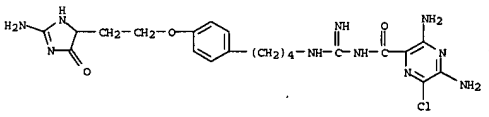
● HCl

RN 847236-96-8 CAPLUS
CN Carbamothioic acid, dimethyl-, S-[4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenyl] ester (9CI) (CA INDEX NAME)



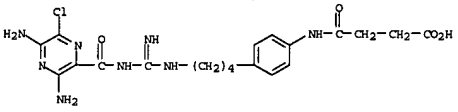
RN 847236-97-9 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[4-[4-[3-[3-[(4-methylphenyl)methyl]-2,4-dioxo-5-oxazolidinyl]propoxy]phenyl]butyl]amino]methyl]-, monohydrochloride (9CI) (CA INDEX NAME)



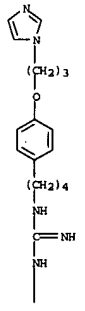


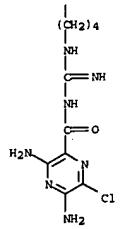
●2 HCl

RN 847237-01-8 CAPLUS
CN Butanoic acid, 4-[[4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenyl]amino]-4-oxo-(9CI) (CA INDEX NAME)



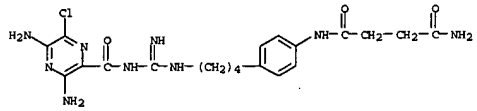
RN 847237-02-9 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[3-(1H-imidazol-1-yl)propoxy]phenyl]butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



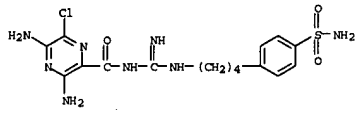


● HCl

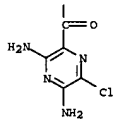
RN 847236-98-0 CAPLUS
CN Butanediamide, N-[4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenyl]-(9CI) (CA INDEX NAME)



RN 847236-99-1 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-(aminosulfonyl)phenyl]butyl]amino]iminomethyl]-6-chloro- (9CI) (CA INDEX NAME)

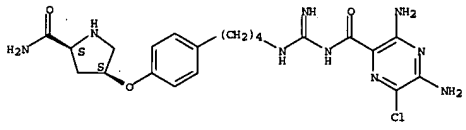


RN 847237-00-7 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[2-(2-amino-4,5-dihydro-5-oxo-1H-imidazol-4-yl)ethoxy]phenyl]butyl]amino]iminomethyl]-6-chloro-, dihydrochloride (9CI) (CA INDEX NAME)



RN 847237-03-0 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[[(3S,5S)-5-(aminocarbonyl)-3-pyrrolidinyl]oxy]phenyl]butyl]amino]iminomethyl]-6-chloro-, dihydrochloride (9CI) (CA INDEX NAME)

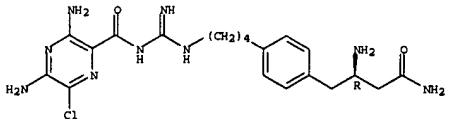
Absolute stereochemistry. Rotation (-).



●2 HCl

RN 847237-04-1 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[(2R)-2,4-diamino-4-oxobutyl]phenyl]butyl]amino]iminomethyl]-,dihydrochloride (9CI) (CA INDEX NAME)

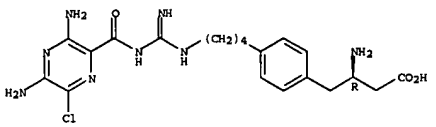
Absolute stereochemistry. Rotation (+).



●2 HCl

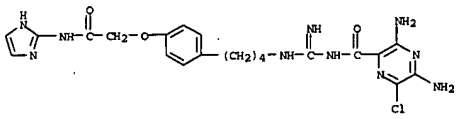
RN 847237-05-2 CAPLUS
CN Benzenebutanoic acid, β-amino-4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]-,dihydrochloride, (βR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

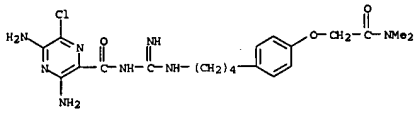


●2 HCl

IT 847354-46-5P 847354-47-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of aminopyrazinoylguanidines as sodium channel blockers)
RN 847354-46-5 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[2-(1H-imidazol-2-ylamino)-2-oxoethoxy]phenyl]butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



RN 847354-47-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[2-(dimethylamino)-2-oxoethoxy]phenyl]butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)

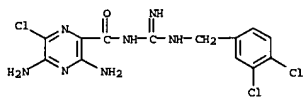


REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

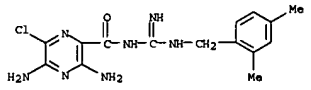
L6 ANSWER 11 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:141259 CAPLUS
DOCUMENT NUMBER: 142:236026
TITLE: Improved electrophysiological screening assays for taste modulators using oocytes that express human ENaC and the use of phenamil to improve the effect of ENaC enhancers in assays using membrane potential reporting dyes
INVENTOR(S): Servant, Guy; Chang, Hong; Redcrow, Cyril; Ray, Sumita; Clark, Imran
PATENT ASSIGNEE(S): Senomyx, Inc., USA
SOURCE: PCT Int. Appl., 118 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005014848	A2	20050217	WO 2004-US21853	20040709
WO 2005014848	A3	20050506		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2004263845	A1	20050217	AU 2004-263845	20040709
CA 2530497	A1	20050217	CA 2004-2530497	20040709
US 2005059094	A1	20050317	US 2004-887233	20040709
EP 1644738	A2	20060412	EP 2004-777748	20040709
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR				
BR 2004012471	A	20060919	BR 2004-12471	20040709
CN 1842709	A	20061004	CN 2004-80024254	20040709
NO 2006000078	A	20060407	NO 2006-78	20060105
			US 2003-485745P P	20030710
PRIORITY APPLN. INFO.:			WO 2004-US21853 W	20040709

AB In one aspect, the present invention relates to a mammalian cell-based high-throughput assay for the profiling and screening of human epithelial sodium channel (hENaC) cloned from a human kidney cDNA library and is also expressed in other tissues including human taste tissue. The present invention further relates to amphibian oocyte-based medium-throughput electrophysiol. assays for identifying human ENaC modulators, preferably ENaC enhancers. Compds. that modulate ENaC function in a cell-based ENaC assay are expected to affect salty taste in humans. The assays described herein have advantages over existing cellular expression systems. In the case of mammalian cells, such assays can be run in standard 96 or 384 well culture plates in high-throughput mode with enhanced assay results being achieved by the use of a compound that inhibits ENaC function, preferably an amiloride derivative such as Phenamil. In the case of the invantive oocyte electrophysiol. assays (two-electrode voltage-clamp technique), these assays facilitate the identification of compds. which specifically modulate human ENaC. The assays of the invention provide a robust screen useful to detect compds. that facilitate (enhance) or inhibit hENaC function. Compds. that enhance or block human ENaC channel activity should thereby modulate salty taste in humans. The nucleotide sequences and the encoded amino acid sequences of α, β, γ, and δ subunits of human ENaC are also disclosed.
IT 1166-01-4, 3',4'-Dichlorobenzamil 2093-13-2, 2',4'-Dimethylbenzamil 118573-60-7, CBDMB
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(ENaC inhibitor; electrophysiol. screening assays for taste modulators using oocytes expressing human ENaC and use of phenamil to improve effect of ENaC enhancers in assays using membrane potential reporting dyes)
RN 1166-01-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



RN 2093-13-2 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2,4-dimethylphenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



RN 118573-60-7 CAPLUS
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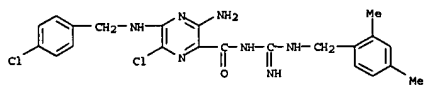
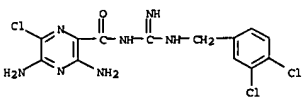


L6 ANSWER 12 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:1156423 CAPLUS
DOCUMENT NUMBER: 142:86608
TITLE: Antiviral acylguanidine compounds, and their therapeutic use
INVENTOR(S): Gage, Peter William; Ewart, Gary Dinneen; Wilson, Lauren Elizabeth; Best, Wayne; Premkumar, Anita
PATENT ASSIGNEE(S): Biotron Limited, Australia
SOURCE: PCT Int. Appl., 215 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004112687	A2	20041229	WO 2004-AU866	20040626
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2004248859	A1	20041229	AU 2004-248859	20040626
CA 2529949	A1	20041229	CA 2004-2529949	20040626
EP 1646371	A2	20060419	EP 2004-737487	20040626
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR				
BR 2004011900	A	20060919	BR 2004-11900	20040626
			AU 2003-903251 A	20030626
PRIORITY APPLN. INFO.:			AU 2003-903850 A	20030725
			AU 2003-904692 A	20030829
			AU 2004-902902 A	20040531
			WO 2004-AU866 W	20040626

OTHER SOURCE(S): MARPAT 142:86608
AB The invention discloses acylguanidine compds. having antiviral activity, as well as methods using these compds. to treat viral infections. Preparation of e.g. cinnamoylguanidine is included.
IT 1166-01-4, 3',4'-Dichlorobenzamil 2088-58-6, 2',4'-DichloroBenzamil hydrochloride 90689-42-2, 2',4'-Dichlorobenzamil
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiviral acylguanidine compds. and therapeutic use)
RN 1166-01-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



RN 2088-58-6 CAPLUS
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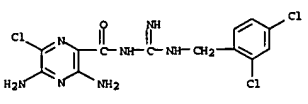
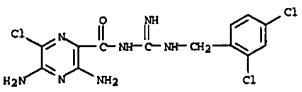


● HCl

RN 90689-42-2 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)

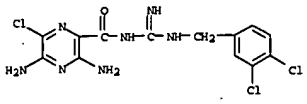


L6 ANSWER 13 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:1050695 CAPLUS
DOCUMENT NUMBER: 142:131445
TITLE: Mechanism of ouabain-induced contractions in guinea-pig tracheal rings
AUTHOR(S): Espinosa-Tanguma, R.; Valle-Aguilera, J. R.; Zarazua-Garcia, O.; Navarro-Huerta, M. P.; Pecina, C.; Sanchez-Armass, S.
CORPORATE SOURCE: Departamentos of Fisiologia y Farmacologia, Facultad de Medicina, Universidad Autonoma de San Luis Potosi, San Luis Potosi, Mex.
SOURCE: Clinical and Experimental Pharmacology and Physiology (2004), 31(10), 710-715
CODEN: CEXPB9; ISSN: 0305-1870
PUBLISHER: Blackwell Publishing Asia Pty Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The aim of the present study was to analyze the mechanism that underlies the force development induced by ouabain (ED100 = 100 μmol/L) in guinea-pig tracheal rings. The dose-response curve showed that concns. of ouabain above 100 μmol/L evoked smaller contractions. Ouabain, at 100 μmol/L, produced two long-lasting consecutive transient contractions. The peak of the first contraction was 750 ± 75 mg, whereas the peak of the second contraction was 280 ± 46 mg. Both contractions induced by ouabain were dependent on extracellular Ca2+. Consistent with this, verapamil (10 μmol/L) inhibited the first and second contractions by 77 and 59%, resp. 3,4-Dichlorobenzamil (20 μmol/L) inhibited the first and second contractions by 68 and 97%, resp. Simultaneous exposure to 15 mmol/L sodium solution and 100 μmol/L ouabain evoked only one transient contraction, larger (987 ± 135 mg) than either of the ouabain-induced contractions. Inhibition of the sarco-endoplasmic reticulum Ca-ATPase with cyclopiazonic acid potentiated the first and second ouabain-induced contractions by 47 and 300%, resp. Atropine (1 μmol/L) inhibited the first and second contractions by 44 and 76%, resp. In conclusion, the results of the present study are relevant to the understanding of the mechanisms by which ouabain (100 μmol/L) contracts guinea-pig tracheal rings. At the muscular level, ouabain induces Ca2+ influx through L-type Ca2+ channels and the reverse mode of the sodium-calcium exchanger. At the nerve terminals, ouabain promotes the release of acetylcholine secondary to the increase in Ca2+ influx mediated by the reverse mode of the sodium-calcium exchanger.

IT 1166-01-4, Dichlorobenzamil
RL: BUU (Biological use, unclassified); PAC (Pharmacological activity); BIOL (Biological study); USES (Uses)
(contraction inhibition by; involvement of extracellular Ca2+, L-type Ca2+ channels, SR Ca2+-ATPase, sodium-calcium exchanger and acetylcholine released from nerve terminals in ouabain-induced contractions in guinea-pig tracheal rings)

RN 1166-01-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 14 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:681400 CAPLUS
DOCUMENT NUMBER: 141:207228
TITLE: Preparation of pyrazinoylguanidines as sodium channel blockers
INVENTOR(S): Johnson, Michael R.
PATENT ASSIGNEE(S): Parion Sciences, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 30 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004162296	A1	20040819	US 2003-367947	20030219
US 6903105	B2	20050607		
AU 2004212962	A1	20040902	AU 2004-212962	20040218
CA 2509981	A1	20040902	CA 2004-2509981	20040218
WO 2004073629	A2	20040902	WO 2004-US4451	20040218
WO 2004073629	A3	20041223		
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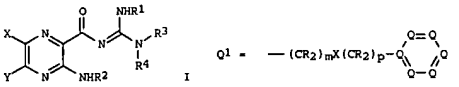
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1599096	A2	20051130	EP 2004-712289	20040218
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
JP 2006518389	T	20060810	JP 2006-503605	20040218
US 2005113388	A1	20050526	US 2004-973447	20041027
US 7030117	B2	20060418		
US 2005113389	A1	20050526	US 2004-973473	20041027
US 6995160	B2	20060207		
US 2005113390	A1	20050526	US 2004-973474	20041027
US 7026325	B2	20060411		
US 2006142581	A1	20060629	US 2005-545083	20050809
US 2006063780	A1	20060323	US 2005-261734	20051031
PRIORITY APPLN. INFO.:			US 2003-367947 A	20030219
			WO 2004-US4451 W	20040218
			US 2004-973474 A1	20041027

OTHER SOURCE(S): MARPAT 141:207228
GI

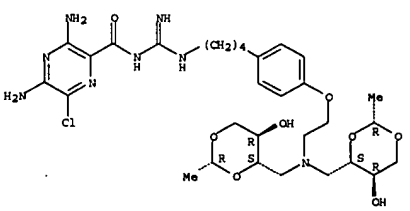


AB Title compds. [I; X = H, halo, CF3, alkyl, (substituted) Ph, alkylthio, phenylalkylthio, alkylsulfonyl, phenylalkylsulfonyl; Y = H, OH, SH, alkoxy, alkylthio, halo, alkyl, (substituted) aryl, N(R2)2; R1 = H, alkyl; R2 = R7, OR8, (CH2)nCO2R7, etc.; n = 0-7; R3, R4 = H, alkyl, hydroxyalkyl, Ph, phenylalkyl, naphthylalkyl, pyridylalkyl, Q1, etc.; ≥1 of R3, R4 = Q; R7 = H, alkyl; R8 = H, alkyl, glucuronide, tetrahydropyranyl, etc.; R = R7, (CH2)nOR8, O-glucuronide, etc.; m, p = 0-10; X = O, NR10, CO, CH(OH), C(:NR10); R5 = (CH2)nNR12R12, (CH2)nNR11R11, N+(R11)3, etc.; o+p = 1-10; R6 = R5, R7, OR8, (CH2)nNR7R10, O-glucuronide, etc.; R10 = H, SO2Me, CO2R7, CONR7R9, COR7, CH2OH, CH2CHOH; R11 = alkyl; R12 = SO2Me, CO2R7, CONR7R9, COR7, CH2OH, CH2CHOH; Q = CR5, CR6, N], were prepared Thus, [2-[4-(4-aminobutyl)benzoylamino]ethyl]carbamicacid tert-Bu ester (preparation given) in MeOH was treated with 1-(3,5-diamino-6-chloropyrazinoyl)-2-methylisothiourea hydroiodide and Et3N followed by 2 h reflux to give 62% protected coupling product, which was stirred 0.5 h in MeOH/HCl to give 100% 4-[4-[N-(3,5-diamino-6-chloropyrazine-2-carbonyl]guanidino]butyl]-N-(2-aminoethyl)benzamide hydrochloride. In canine bronchial epithelia, I showed 17.2-170 times the Na channel blocking activity of Amiloride.

IT 587880-62-4P 587880-69-1P 742101-90-2P
742101-92-4P 742101-93-5P 742101-94-6P
742101-95-7P 742101-96-8P 742101-97-9P
742101-98-0P 742101-99-1P 742102-00-7P
742102-01-8P 742102-02-9P 742102-03-0P
742102-04-1P 742102-05-2P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(claimed compound; preparation of pyrazinoylguanidines as sodium channel blockers)

RN 587880-62-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[2-[bis[[(2R,4S,5R)-5-hydroxy-2-methyl-1,3-dioxan-4-yl]methyl]amino]ethoxy]phenyl]butyl]amino]iminomethyl]-6-chloro- (9CI) (CA INDEX NAME)

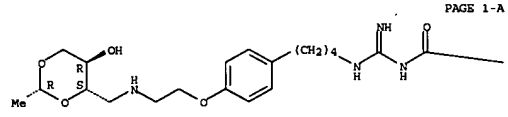
Absolute stereochemistry. Rotation (-).



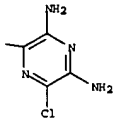
RN 587880-69-1 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[2-[[[(2R,4S,5R)-5-hydroxy-2-methyl-1,3-dioxan-4-yl]methyl]amino]ethoxy]phenyl]butyl]amino]iminomethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



RN 742101-90-2 CAPLUS
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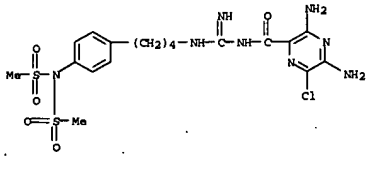
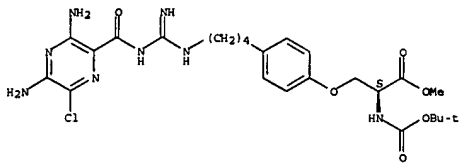


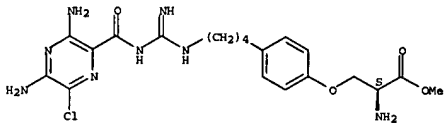
RN 742101-92-4 CAPLUS
CN L-Serine, O-[4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenyl]-N-[(1,1-dimethylethoxy)carbonyl]-methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 742101-93-5 CAPLUS
CN L-Serine, O-[4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminom ethyl]amino]butyl]phenyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 742101-94-6 CAPLUS
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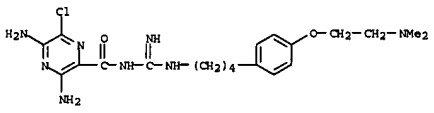

RN 742101-95-7 CAPLUS
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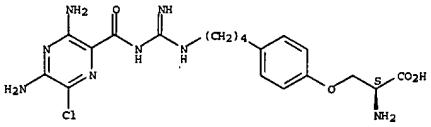
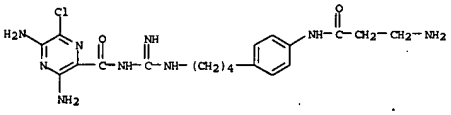
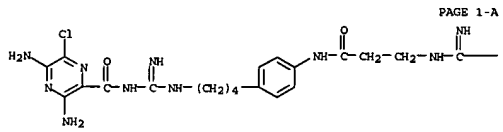
Absolute stereochemistry.





RN 742102-00-7 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[[3-[(aminoiminomethyl)amino]-1-oxopropyl]amino]phenyl]butyl]amino]iminomethyl]-6-chloro-(9CI) (CA INDEX NAME)

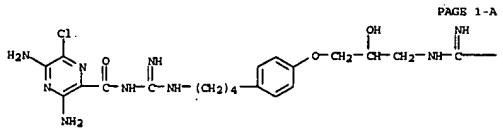


PAGE 1-A

PAGE 1-B

— NH_2

RN 742102-01-8 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[3-[(aminoiminomethyl)amino]-2-hydroxypropoxy]phenyl]butyl]amino]iminomethyl]-6-chloro-(9CI) (CA INDEX NAME)



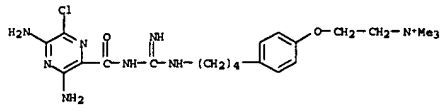
PAGE 1-A

PAGE 1-B

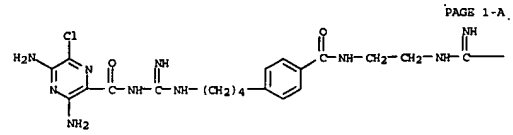
— NH_2

RN 742102-02-9 CAPLUS
CN D-Glucitol, 1,1'-[[2-[4-[4-[[[[(3,5-diamino-6-

RN 742101-96-8 CAPLUS
CN Ethanaminium, 2-[4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenoxy]-N,N,N-trimethyl-(9CI) (CA INDEX NAME)



RN 742101-97-9 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[[[2-[(aminoiminomethyl)amino]ethyl]amino]carbonyl]phenyl]butyl]amino]iminomethyl]-6-chloro- (9CI) (CA INDEX NAME)

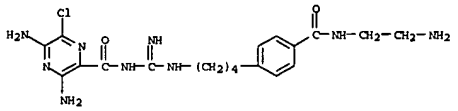


PAGE 1-A

PAGE 1-B

— NH_2

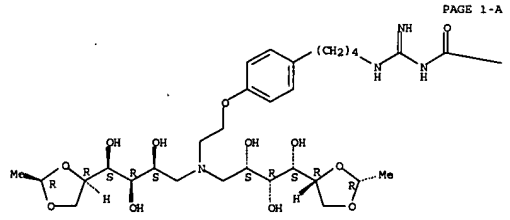
RN 742101-98-0 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[[(2-aminoethyl)amino]carbonyl]phenyl]butyl]amino]iminomethyl]-6-chloro (9CI) (CA INDEX NAME)



RN 742101-99-1 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[(3-amino-1-oxopropyl)amino]phenyl]butyl]amino]iminomethyl]-6-chloro-(9CI) (CA INDEX NAME)

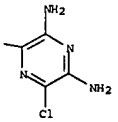
chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenoxy]ethyl]imino]bis[1-deoxy-5,6-O-(1R)-ethylidene-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



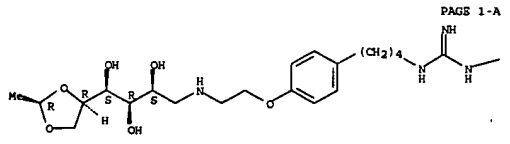
PAGE 1-A

PAGE 1-B



RN 742102-03-0 CAPLUS
CN D-Glucitol, 1-[[2-[4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenoxy]ethyl]amino]-1-deoxy-5,6-O-(1R)-ethylidene-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



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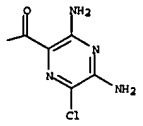
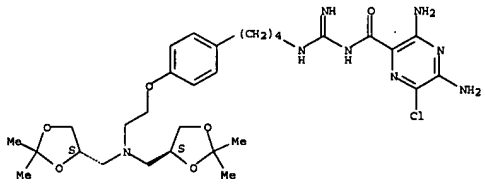
PAGE 1-B



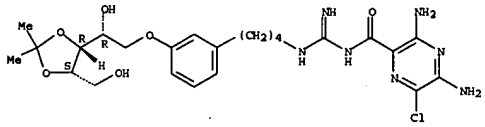
RN 742102-04-1 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[2-[bis[[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl]amino]ethoxy]phenyl]butyl]amino]iminomethyl]-6-chloro- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



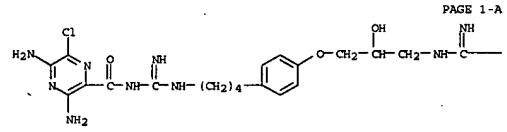
RN 742102-05-2 CAPLUS
CN D-Ribitol, 5-O-[3-[4-[[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenyl]-2,3-O-(1-methylethylidene)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 742102-06-3P 742102-07-4P 742102-09-6P
742102-11-0P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of pyrazinoylguanidines as sodium channel blockers)
RN 742102-06-3 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[[(2-aminoethyl)amino]carbonyl]phenyl]butyl]amino]iminomethyl]-6-chloro-, monohydrochloride (9CI) (CA INDEX NAME)

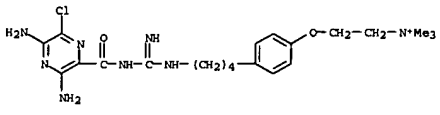
PAGE 1-A



● HCl

PAGE 1-B

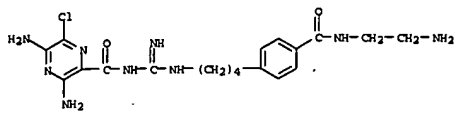
RN 742102-11-0 CAPLUS
CN Ethanaminium, 2-[4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenoxy]-N,N,N-trimethyl-,chloride, monohydrochloride (9CI) (CA INDEX NAME)



● Cl⁻

● HCl

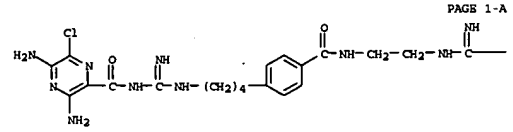
IT 742102-34-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of pyrazinoylguanidines as sodium channel blockers)
RN 742102-34-7 CAPLUS
CN Ethanaminium, 2-[4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenoxy]-N,N,N-trimethyl-,chloride (9CI) (CA INDEX NAME)



● HCl

RN 742102-07-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[[[2-[(aminoiminomethyl)amino]ethyl]amino]carbonyl]phenyl]butyl]amino]iminomethyl]-6-chloro-, monohydrochloride (9CI) (CA INDEX NAME)

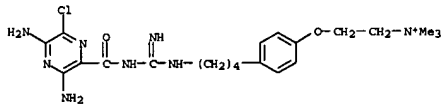
PAGE 1-A



● HCl

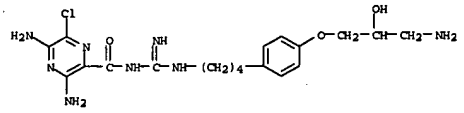
PAGE 1-B

RN 742102-09-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[3-[(aminoiminomethyl)amino]-2-hydroxypropoxy]phenyl]butyl]amino]iminomethyl]-6-chloro-, monohydrochloride (9CI) (CA INDEX NAME)



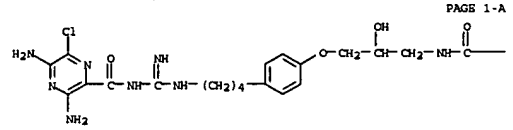
● Cl⁻

IT 587879-47-8P 587880-14-6P 742102-18-7P
742102-19-8P 742102-24-5P 742102-32-5P
742102-33-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of pyrazinoylguanidines as sodium channel blockers)
RN 587879-47-8 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-(3-amino-2-hydroxypropoxy)phenyl]butyl]amino]iminomethyl]-6-chloro-(9CI) (CA INDEX NAME)



RN 587880-14-6 CAPLUS
CN Carbamic acid, [3-[4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenoxy]-2-hydroxypropyl]-,1,1-dimethylethyl ester (9CI) (CA INDEX NAMES)

PAGE 1-A

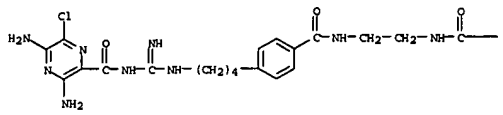


PAGE 1-B

RN 742102-18-7 CAPLUS
CN Carbamic acid, [2-[[4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]benzoyl]amino]ethyl]-,1,1-dimethylethyl ester

(9CI) (CA INDEX NAME)

PAGE 1-A

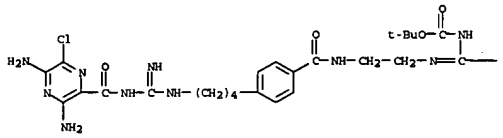


PAGE 1-B

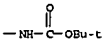
—OBu-t

RN 742102-19-8 CAPLUS
CN Carbamic acid, [[2-[[4-[4-[[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]benzoyl]amino]ethyl]carbonimidoyl]bis-, bis(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)

PAGE 1-A

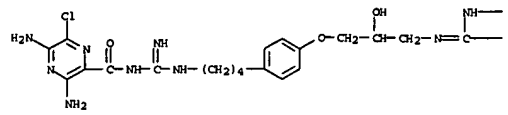


PAGE 1-B

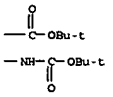


RN 742102-24-5 CAPLUS
CN Carbamic acid, [[3-[4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenoxy]-2-hydroxypropyl]carbonimidoyl]bis-, bis(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)

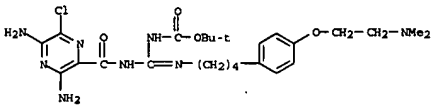
PAGE 1-A



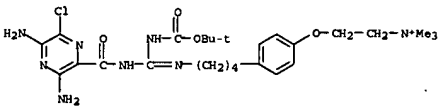
PAGE 1-B



RN 742102-32-5 CAPLUS
CN Carbamic acid, [[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino][[4-[4-[2-(dimethylamino)ethoxy]phenyl]butyl]amino]methylene]-,1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



RN 742102-33-6 CAPLUS
CN Ethanaminium, 2-[4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino][[(1,1-dimethylethoxy)carbonyl]amino]methylene]amino]butyl]phenoxy]-N,N,N-trimethyl-, iodide (9CI) (CA INDEX NAME)



● I⁻

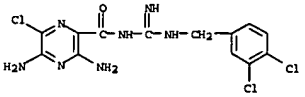
REFERENCE COUNT: 238 THERE ARE 238 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 15 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:547007 CAPLUS
DOCUMENT NUMBER: 141:64618
TITLE: Amiloride kills malignant glioma cells independent of its inhibition of the sodium-hydrogen exchanger
AUTHOR(S): Hegde, Manu; Roscoe, Jane; Cala, Peter; Gorin, Fredric
CORPORATE SOURCE: Department of Neurology, School of Medicine, University of California, Davis, CA, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (2004), 310(1), 67-74
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Previously, we demonstrated that malignant glioma cell lines have increased intracellular pH (pHi) as a result of increased activities of the type I sodium/hydrogen exchanger (NHE1). This alkalotic pHi of 7.2 to 7.4 is favorable for augmented glycolysis, DNA synthesis, and cell cycle progression. Conversely, redns. in pHi have been associated with reduced rates of proliferation in transformed cell types. The effects of reducing pHi directly and by NHE1 inhibition on human malignant glioma cells were systematically compared with those on primary rat astrocytes. Neither cariporide, nor direct acidification to pHi 6.9 altered the proliferative rates or viabilities of human U87 or U118 malignant glioma cell lines. However, amiloride significantly impaired glioma cell proliferation and viability while not affecting astrocytes at concns. (500 μM) that exceeded its inhibition of NHE1 in glioma cells (IC50 = 17 μM). Preventing a reduction of pHi did not alter the drug's antiproliferative and cytotoxic effects on glioma cells. These findings indicated that amiloride's cytotoxic effects on glioma cells are independent of its ability to inhibit NHE1 or to reduce intracellular pHi. The amiloride derivative 2,4 dichlorobenzamil (DCB) inhibits the sodium-calcium exchanger (NCX) and was both antiproliferative and cytotoxic to glioma cells at low doses (20 μM). By contrast, KB-R7943 [(2-[2-[4-nitrobenzyloxy]phenyl]ethyl)-isothioureamethanesulfonate]preferentially blocks sodium-dependent calcium influx by NCX (reverse mode) and was nontoxic to glioma cells. It is proposed that DCB (20 μM) and amiloride (500 μM) impair calcium efflux by NCX, leading to elevations of intracellular calcium that initiate a morphol. necrotic, predominantly caspase-independent glioma cell death.

IT 1166-01-4, Dichlorobenzamil
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(amiloride kills malignant glioma cells independent of inhibition of sodium-hydrogen exchanger)

RN 1166-01-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



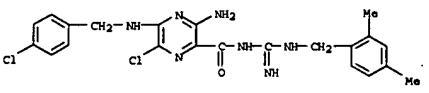
REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 16 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:126082 CAPLUS
DOCUMENT NUMBER: 140:319421
TITLE: Evidence for a protective role played by the Na+/Ca2+ exchanger in cerebral ischemia induced by middle cerebral artery occlusion in male rats
AUTHOR(S): Pignataro, Giuseppe; Tortiglione, Anna; Scorziello, Antonella; Giaccio, Lucia; Secondo, Agnese; Severino, Beatrice; Santagada, Vincenzo; Caliendo, Giuseppe; Amoroso, Salvatore; Di Renzo, Gianfranco; Annunziato, Lucio
CORPORATE SOURCE: Department of Neuroscience, Division of Pharmacology, University of Naples "Federico II", Naples, 80131, Italy
SOURCE: Neuropharmacology (2004), 46(3), 439-448
CODEN: NEPHBW; ISSN: 0028-3908
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal.
LANGUAGE: English

AB In the present paper, the role played by Na+/Ca2+ exchanger (NCX) in focal cerebral ischemia was investigated. To this aim, permanent middle cerebral artery occlusion (pMCAO) was performed in male rats. The effects on the infarct volume of some inhibitors, such as tyrosine-6 glycosylated form of the exchanger inhibitory peptide (GLU-XIP), benzamil derivative (CB-DMB) and diarylaminopropylamine derivative (bepridil), and of the NCX activator, FeCl3, were examined FeCl3, CB-DMB, bepridil and GLU-XIP, a modified peptide synthesized in our laboratory in order to facilitate its entrance into the cells through the glucose transporter, were intracerebroventricularly (icv) infused. FeCl3 (10 μg/kg) was able to reduce the extension of brain infarct volume This effect was counteracted by the concomitant icv administration of CB-DMB (120 μg/kg). All NCX inhibitors, GLU-XIP, CB-DMB and bepridil, caused a worsening of the brain infarct lesion. These results suggest that a stimulation of NCX activity may help neurons and glial cells that are not irreversibly damaged in the penumbral zone to survive, whereas its pharmacol. blockade can compromise their survival.

IT 118573-60-7, CB-DMB
RL: BUU (Biological use, unclassified); PAC (Pharmacological activity); BIOL (Biological study); USES (Uses)
(Na+/Ca2+ exchanger and its inhibitors and activators in cerebral ischemia induced by middle cerebral artery occlusion)

RN 118573-60-7 CAPLUS
CN Pyrazinecarboxamide, 3-amino-6-chloro-5-[[(4-chlorophenyl)methyl]amino]-N-[[[(2,4-dimethylphenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 17 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:678615 CAPLUS
DOCUMENT NUMBER: 139:191482
TITLE: Sodium channel blockers
INVENTOR(S): Johnson, Michael R.
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 66 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003070184	A2	20030828	WO 2003-US4823	20030219
WO 2003070184	A3	20040617		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
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US 6858614	B2	20050222		
CA 2476837	A1	20030828	CA 2003-2476837	20030219
AU 2003215286	A1	20030909	AU 2003-215286	20030219
EP 1485359	A2	20041215	EP 2003-711105	20030219
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
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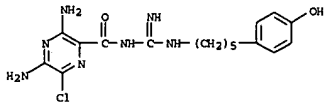
US 2004204424	A1	20041014	US 2004-828235	20040421
PRIORITY APPLN. INFO.:			US 2002-76551 A	20020219
			WO 2003-US4823 W	20030219

OTHER SOURCE(S): MARPAT 139:191482

AB The present invention relates to sodium channel blockers (Markush structures are included). The present invention also includes a variety of methods of treatment using these novel sodium channel blockers.

IT 583825-17-6P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(sodium channel blockers for therapy of pulmonary and other diseases)

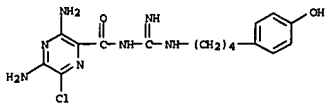
RN 583825-17-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[5-(4-hydroxyphenyl)pentyl]amino]iminomethyl]-,monohydrochloride (9CI) (CA INDEX NAME)



● HCl

IT 583825-14-3P 583825-15-4P 583825-16-5P 583825-18-7P 583825-19-8P 583825-23-4P 583825-24-5P 583825-25-6P 583825-26-7P 583825-33-6P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(sodium channel blockers for therapy of pulmonary and other diseases)

RN 583825-14-3 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-(4-hydroxyphenyl)butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



RN 583825-15-4 CAPLUS
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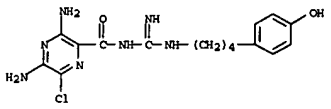

● HCl

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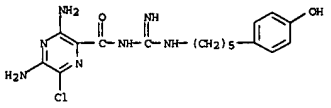
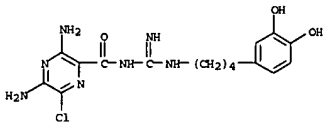
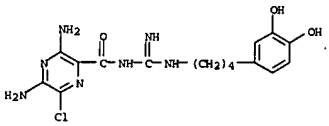


RN 583825-18-7 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-(3,4-dihydroxyphenyl)butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)

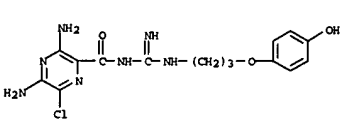


RN 583825-19-8 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-(3,4-dihydroxyphenyl)butyl]amino]iminomethyl]-,monohydrochloride (9CI) (CA INDEX NAME)

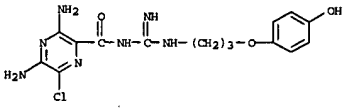


● HCl

RN 583825-23-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[3-(4-hydroxyphenoxy)propyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)

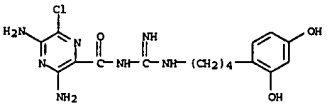


RN 583825-24-5 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[3-(4-hydroxyphenoxy)propyl]amino]iminomethyl]-,monohydrochloride (9CI) (CA INDEX NAME)

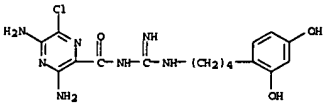


● HCl

RN 583825-25-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-(2,4-dihydroxyphenyl)butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



RN 583825-26-7 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-(2,4-dihydroxyphenyl)butyl]amino]iminomethyl]-,monohydrochloride (9CI) (CA INDEX NAME)



● HCl

RN 583825-33-6 CAPLUS
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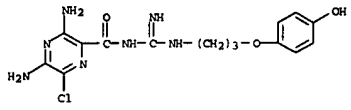

● HBr

L6 ANSWER 18 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:678613 CAPLUS
DOCUMENT NUMBER: 139:214488
TITLE: Preparation of diaminopyrazines as sodium channel blockers for promoting the hydration of mucosal surfaces
INVENTOR(S): Johnson, Michael R.
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 139 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

THIS APPLICATION

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003070182	A2	20030828	WO 2003-US4817	20030219
WO 2003070182	A3	20031224		
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US 6858615	B2	20050222		
CA 2476430	A1	20030828	CA 2003-2476430	20030219
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			WO 2003-US4817 W	20030219

OTHER SOURCE(S): MARPAT 139:214488
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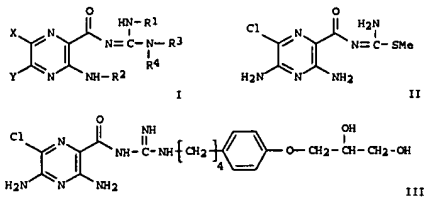


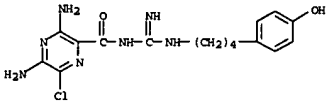
I II

III

AB Title compds. I [X = H, halo, CF3, etc.; Y = H, OH, SH, etc.; R1 = H, alkyl; R2 = R7, (CH2)mOR8, (CH2)mNR7R10, etc.; R3, R4 = H, alkyl, hydroxyalkyl, etc. with provisos; R7 = H, alkyl; R8 = H, alkyl, glucuronide, etc.; R10 = H, SO2CH3, CO2R7, etc.; m = 1-7] and their pharmaceutically acceptable salts were prepared For example, condensation of thiourea II hydroiodide and 4-[(2,3-dihydroxypropyloxy)phenyl]butylamine, e.g., prepared from 4-(4-hydroxyphenyl)butylamine in 4-steps, afforded diaminopyrazine III hydrochloride in 53% yield. In canine bronchial epithelia sodium channel blocking activity assays, 12-examples of compds. I exhibited fold-enhancement values relative to amiloride ranging from 11.2-124, e.g., the fold-enhancement value of diaminopyrazine III hydrochloride was 124. Compds. I are claimed useful as antiasthmatics, laxatives, antihypertensives, etc.

IT 583825-15-4P 587879-60-5P 587880-56-6P
587880-57-7P 587880-58-8P 587880-69-1P
587880-76-0P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(drug candidate; preparation of diaminopyrazines as sodium channel blockers for promoting the hydration of mucosal surfaces)

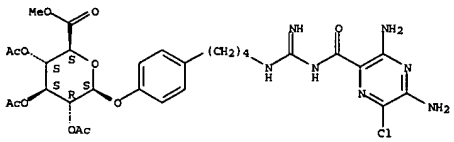
RN 583825-15-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-(4-hydroxyphenyl)butyl]amino]iminomethyl]-,monohydrochloride (9CI) (CA INDEX NAME)



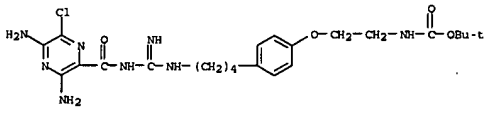
● HCl

RN 587879-60-5 CAPLUS
CN β-D-Glucopyranosiduronic acid, 4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenyl methyl ester, 2,3,4-triacetate (9CI) (CA INDEX NAME)

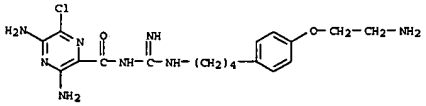
Absolute stereochemistry.



RN 587880-56-6 CAPLUS
CN Carbamic acid, [2-[4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenoxy]ethyl]-,1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

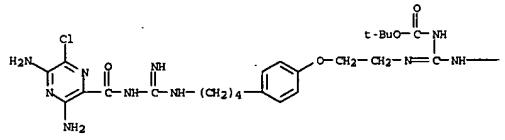


RN 587880-57-7 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-(2-aminoethoxy)phenyl]butyl]amino]iminomethyl]-6-chloro-(9CI) (CA INDEX NAME)



RN 587880-58-8 CAPLUS
CN Carbamic acid, [[2-[4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenoxy]ethyl]carbonimidoyl]bis-, bis(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)

PAGE 1-A

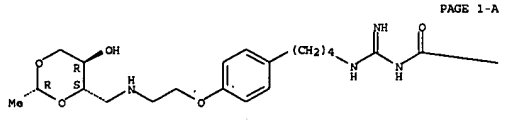


PAGE 1-B

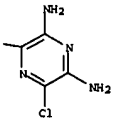
RN 587880-69-1 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[2-[[[(2R,4S,5R)-5-hydroxy-2-methyl-1,3-dioxan-4-yl]methyl]amino]ethoxy]phenyl]butyl]amino]iminomethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

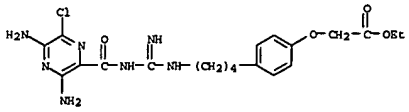
PAGE 1-A



PAGE 1-B



RN 587880-76-0 CAPLUS
CN Acetic acid, [4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenoxy]-, ethyl ester (9CI) (CA INDEX NAME)



IT 583825-14-3P 587879-24-1P 587879-25-2P
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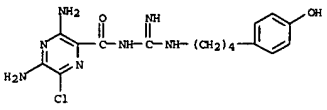
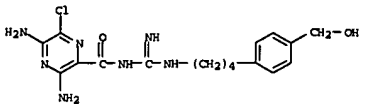
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; preparation of diaminopyrazines as sodium channel blockers for promoting the hydration of mucosal surfaces)

RN 583825-14-3 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-(4-hydroxyphenyl)butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



RN 587879-24-1 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[4-(hydroxymethyl)phenyl]butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



RN 587879-25-2 CAPLUS
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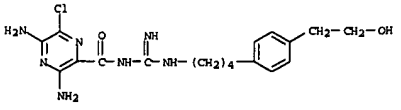
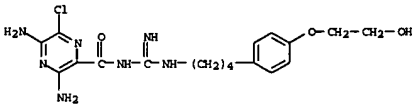
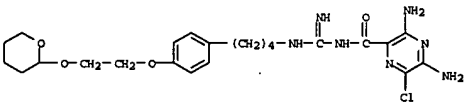


RN 587879-26-3 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-(2-hydroxyethoxy)phenyl]butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



RN 587879-27-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[4-[4-[2-[(tetrahydro-2H-pyran-2-yl)oxy]ethoxy]phenyl]butyl]amino]methyl]-(9CI) (CA INDEX NAME)



RN 587879-28-5 CAPLUS
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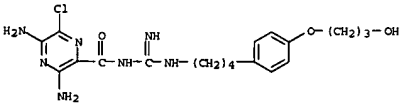
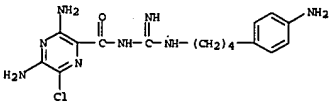
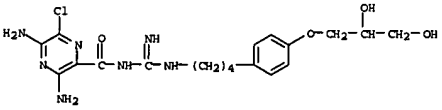


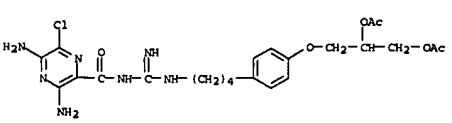
RN 587879-29-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-(4-aminophenyl)butyl]amino]iminomethyl]-6-chloro- (9CI) (CA INDEX NAME)



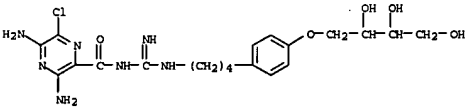
RN 587879-32-1 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-(2,3-dihydroxypropoxy)phenyl]butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



RN 587879-33-2 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[2,3-bis(acetyloxy)propoxy]phenyl]butyl]amino]iminomethyl]-6-chloro (9CI) (CA INDEX NAME)

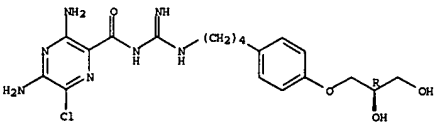


RN 587879-34-3 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[4-[4-(2,3,4-trihydroxybutoxy)phenyl]butyl]amino]methyl]-(9CI) (CA INDEX NAME)



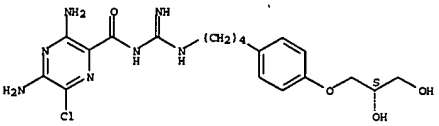
RN 587879-35-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[(2R)-2,3-dihydroxypropoxy]phenyl]butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

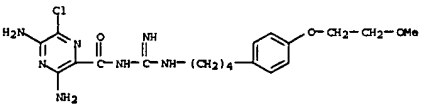


RN 587879-36-5 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[(2S)-2,3-dihydroxypropoxy]phenyl]butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

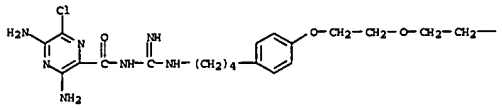


RN 587879-37-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[4-[4-(2-methoxyethoxy)phenyl]butyl]amino]methyl]-(9CI) (CA INDEX NAME)



RN 587879-39-8 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[4-[4-[2-(2-methoxyethoxy)ethoxy]phenyl]butyl]amino]methyl]-(9CI) (CA INDEX NAME)

PAGE 1-A

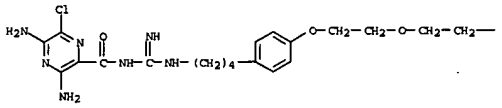


PAGE 1-B

—OMe

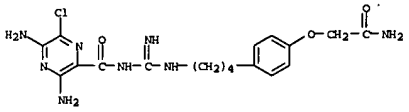
RN 587879-42-3 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[4-[4-(3,6,9,12-tetraoxatridec-1-yloxy)phenyl]butyl]amino]methyl]-(9CI) (CA INDEX NAME)

PAGE 1-A

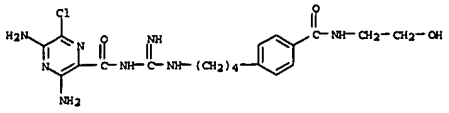


PAGE 1-B

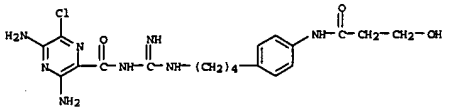
RN 587879-43-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-(2-amino-2-oxoethoxy)phenyl]butyl]amino]iminomethyl]-6-chloro-(9CI) (CA INDEX NAME)



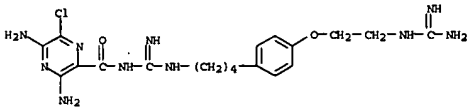
RN 587879-44-5 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[[(2-hydroxyethyl)amino]carbonyl]phenyl]butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



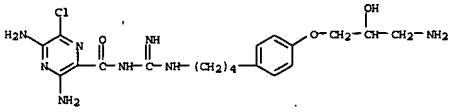
RN 587879-45-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[(3-hydroxy-1-oxopropyl)amino]phenyl]butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



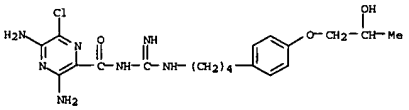
RN 587879-46-7 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[2-[(aminoiminomethyl)amino]ethoxy]phenyl]butyl]amino]iminomethyl]-6-chloro-(9CI) (CA INDEX NAME)



RN 587879-47-8 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-(3-amino-2-hydroxypropoxy)phenyl]butyl]amino]iminomethyl]-6-chloro-(9CI) (CA INDEX NAME)



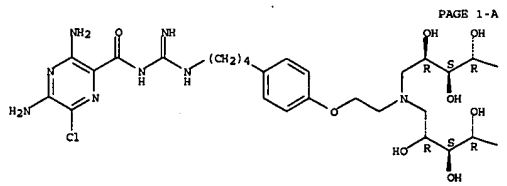
RN 587879-48-9 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-(2-hydroxypropoxy)phenyl]butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



RN 587879-49-0 CAPLUS
CN D-Arabinitol, 1,1'-[[2-[4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenoxy]ethyl]imino]bis[1-deoxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

PAGE 1-A

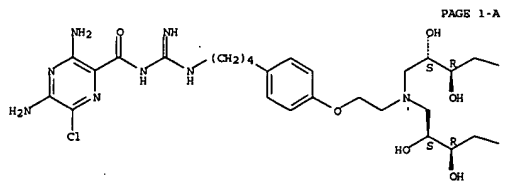


PAGE 1-B

RN 587879-50-3 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[2-[bis[(2S,3R)-2,3,4-trihydroxybutyl]amino]ethoxy]phenyl]butyl]amino]iminomethyl]-6-chloro-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

PAGE 1-A

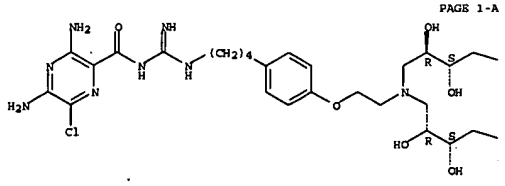


PAGE 1-B

RN 587879-51-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[2-[bis[(2R,3S)-2,3,4-trihydroxybutyl]amino]ethoxy]phenyl]butyl]amino]iminomethyl]-6-chloro-(9CI) (CA INDEX NAME)

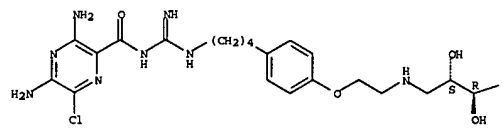
Absolute stereochemistry. Rotation (+).

PAGE 1-A

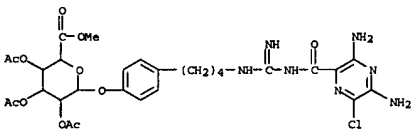


RN 587879-52-5 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[4-[4-[2-[[(2S,3R)-2,3,4-trihydroxybutyl]amino]ethoxy]phenyl]butyl]amino]methyl] (9CI) (CA INDEX NAME)

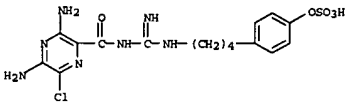
Absolute stereochemistry.



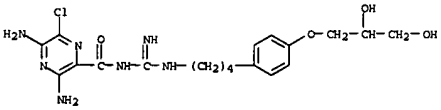
RN 587879-53-6 CAPLUS
CN Hexopyranosiduronic acid, 4-[4-[[[[(3,5-diamino-6-chloropyrazinyl]carbonyl]amino]iminomethyl]amino]butyl]phenyl methyl ester, 2,3,4-triacetate (9CI) (CA INDEX NAME)



RN 587879-54-7 CAPLUS

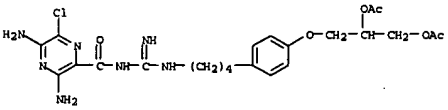


RN 587879-57-0 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-(2,3-dihydroxypropoxy)phenyl]butyl]amino]iminomethyl]-,monohydrochloride (9CI) (CA INDEX NAME)



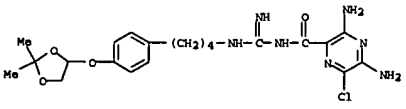
● HCl

RN 587879-58-1 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[2,3-bis(acetyloxy)propoxy]phenyl]butyl]amino]iminomethyl]-6-chloro-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

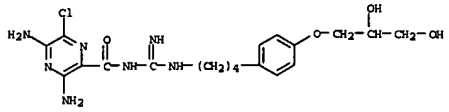
RN 587879-59-2 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[(2,2-dimethyl-1,3-dioxolan-4-yl)oxy]phenyl]butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-(2,3-dihydroxypropoxy)phenyl]butyl]amino]iminomethyl]-,monomethanesulfonate (salt) (9CI) (CA INDEX NAME)

CM 1

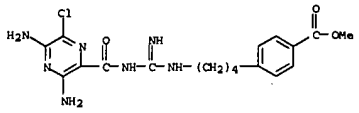
CRN 587879-32-1
CMF C19 H26 Cl N7 O4



CM 2

CRN 75-75-2
CMF C H4 O3 S

RN 587879-55-8 CAPLUS
CN Benzoic acid, 4-[4-[[[[(3,5-diamino-6-chloropyrazinyl]carbonyl]amino]iminomethyl]amino]butyl]-, methyl ester, monohydrochloride (9CI) (CA INDEX NAME)

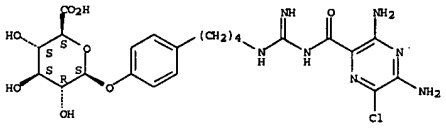


● HCl

RN 587879-56-9 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[4-[4-(sulfooxy)phenyl]butyl]amino]methyl]-(9CI) (CA INDEX NAME)

RN 587879-61-6 CAPLUS
CN β-D-Glucopyranosiduronic acid, 4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenyl (9CI) (CA INDEX NAME)

Absolute stereochemistry.

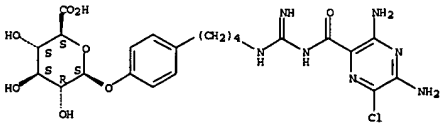


RN 587879-62-7 CAPLUS
CN β-D-Glucopyranosiduronic acid, 4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenyl, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 587879-61-6
CMF C22 H28 Cl N7 O8

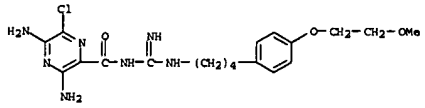
Absolute stereochemistry.



CM 2

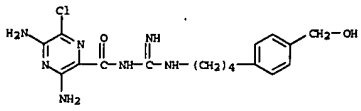
CRN 76-05-1
CMF C2 H F3 O2

RN 587879-63-8 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[4-[4-(2-methoxyethoxy)phenyl]butyl]amino]methyl]-,monohydrochloride (9CI) (CA INDEX NAME)



● HCl

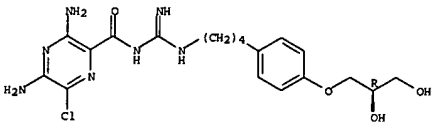
RN 587879-64-9 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-(hydroxymethyl)phenyl]butyl]amino]iminomethyl]-,monohydrochloride (9CI) (CA INDEX NAME)



● HCl

RN 587879-65-0 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[(2R)-2,3-dihydroxypropoxy]phenyl]butyl]amino]iminomethyl]-,monohydrochloride (9CI) (CA INDEX NAME)

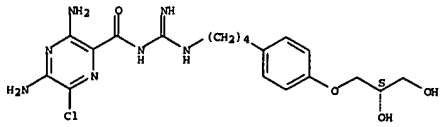
Absolute stereochemistry. Rotation (-).



● HCl

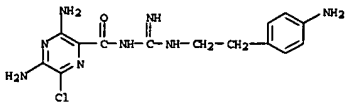
RN 587879-66-1 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[(2S)-2,3-dihydroxypropoxy]phenyl]butyl]amino]iminomethyl]-,monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



● HCl

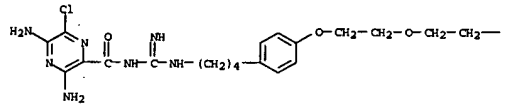
RN 587879-67-2 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[2-(4-aminophenyl)ethyl]amino]iminomethyl]-6-chloro-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

RN 587879-68-3 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[4-[4-[2-(2-methoxyethoxy)ethoxy]phenyl]butyl]amino]methyl]-,monohydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



● HCl

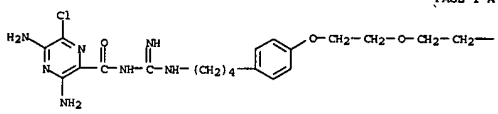
PAGE 1-B

—OMe

RN 587879-69-4 CAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[4-[4-(3,6,9,12-tetraoxatridec-1-yloxy)phenyl]butyl]amino]methyl]-,dihydrochloride (9CI) (CA INDEX NAME)

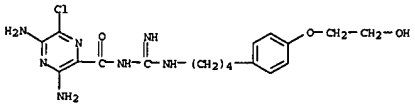
PAGE 1-A



●2 HCl

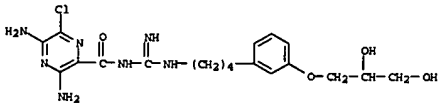
PAGE 1-B

RN 587879-70-7 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-(2-hydroxyethoxy)phenyl]butyl]amino]iminomethyl]-,monohydrochloride (9CI) (CA INDEX NAME)

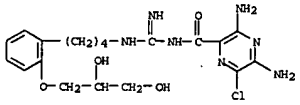


● HCl

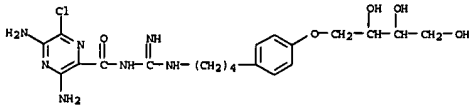
RN 587879-71-8 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[3-(2,3-dihydroxypropoxy)phenyl]butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



RN 587879-72-9 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[2-(2,3-dihydroxypropoxy)phenyl]butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)

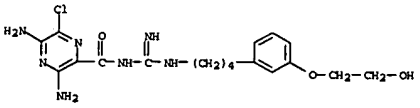


RN 587879-73-0 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[4-[4-(2,3,4-trihydroxybutoxy)phenyl]butyl]amino]methyl]-,monohydrochloride (9CI) (CA INDEX NAME)

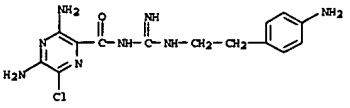


● HCl

RN 587879-74-1 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[3-(2-hydroxyethoxy)phenyl]butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)

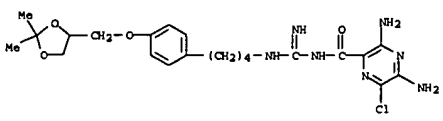


RN 587879-75-2 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[2-(4-aminophenyl)ethyl]amino]iminomethyl]-6-chloro- (9CI) (CA INDEX NAME)



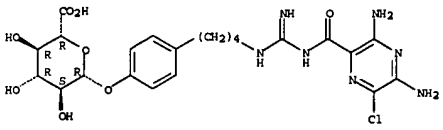
RN 587879-76-3 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[(2,2-dimethyl-1,3-

dioxolan-4-yl)methoxy]phenyl]butyl]amino]iminomethyl]·(9CI) (CA INDEX NAME)



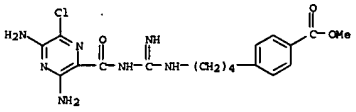
RN 587879-78-5 CAPLUS
CN β-L-Glucopyranosiduronic acid, 4-[4-[[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenyl monosodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.

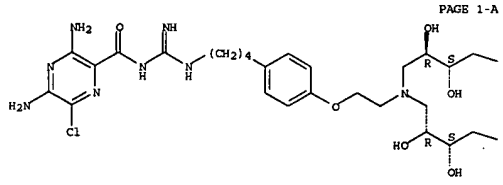


● Na

RN 587879-79-6 CAPLUS
CN Benzoic acid, 4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]imino methyl]amino]butyl]-, methyl ester (9CI) (CA INDEX NAME)



RN 587879-80-9 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[2-[(aminoiminomethyl)amino]ethoxy]phenyl]butyl]amino]iminomethyl]-6-chloro-, dihydrochloride (9CI) (CA INDEX NAME)



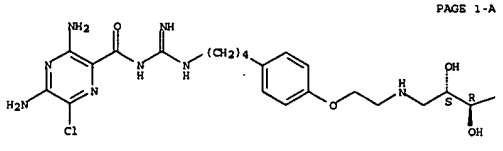
●2 HCl

PAGE 1-B

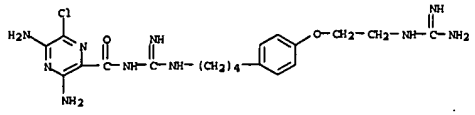
RN 587879-83-2 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[4-[4-[2-[[(2S,3R)-2,3,4-trihydroxybutyl]amino]ethoxy]phenyl]butyl]amino]methyl]-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



●2 HCl

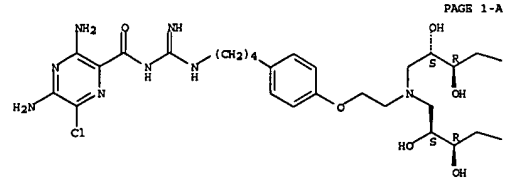


●2 HCl

RN 587879-81-0 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[2-[bis[(2S,3R)-2,3,4-trihydroxybutyl]amino]ethoxy]phenyl]butyl]amino]iminomethyl]-6-chloro-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

PAGE 1-A



●2 HCl

PAGE 1-B

RN 587879-82-1 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[2-[bis[(2R,3S)-2,3,4-trihydroxybutyl]amino]ethoxy]phenyl]butyl]amino]iminomethyl]-6-chloro-, dihydrochloride (9CI) (CA INDEX NAME)

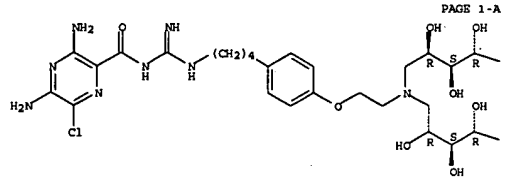
Absolute stereochemistry. Rotation (+).

PAGE 1-B

RN 587879-84-3 CAPLUS
CN D-Arabinitol, 1,1'-[[2-[4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenoxy]ethyl]imino]bis[1-deoxy-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

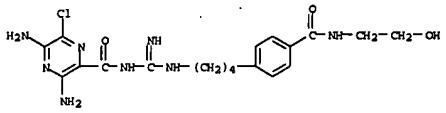
PAGE 1-A



●2 HCl

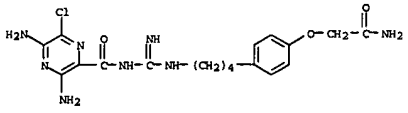
PAGE 1-B

RN 587879-85-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[[(2-hydroxyethyl)amino]carbonyl]phenyl]butyl]amino]iminomethyl]-, monohydrochloride (9CI) (CA INDEX NAME)



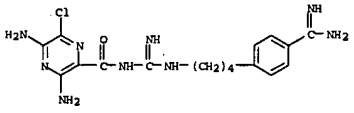
● HCl

RN 587879-86-5 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-(2-amino-2-oxoethoxy)phenyl]butyl]amino]iminomethyl]-6-chloro-, monohydrochloride (9CI) (CA INDEX NAME)

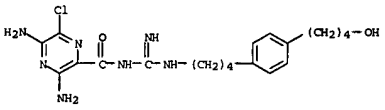


● HCl

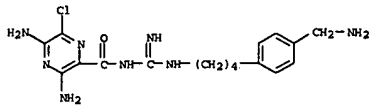
RN 587879-87-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[amino[[4-[4-(aminoiminomethyl)phenyl]butyl]amino]methylene]-6-chloro-(9CI) (CA INDEX NAME)



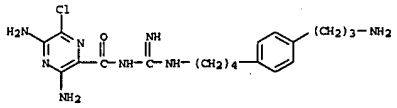
RN 587879-88-7 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-(4-hydroxybutyl)phenyl]butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



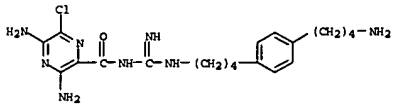
RN 587879-89-8 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-(aminomethyl)phenyl]butyl]amino]iminomethyl]-6-chloro- (9CI) (CA INDEX NAME)



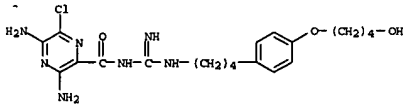
RN 587879-90-1 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-(3-aminopropyl)phenyl]butyl]amino]iminomethyl]-6-chloro-(9CI) (CA INDEX NAME)



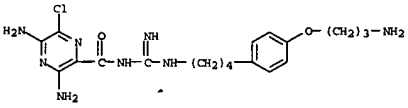
RN 587879-91-2 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-(4-aminobutyl)phenyl]butyl]amino]iminomethyl]-6-chloro-(9CI) (CA INDEX NAME)



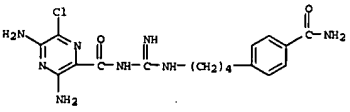
RN 587879-92-3 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-(4-hydroxybutoxy)phenyl]butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



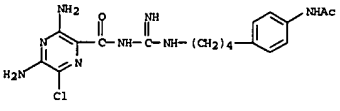
RN 587879-93-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-(3-aminopropoxy)phenyl]butyl]amino]iminomethyl]-6-chloro-(9CI) (CA INDEX NAME)



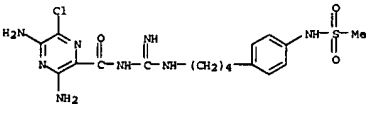
RN 587879-94-5 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-(aminocarbonyl)phenyl]butyl]amino]iminomethyl]-6-chloro- (9CI) (CA INDEX NAME)



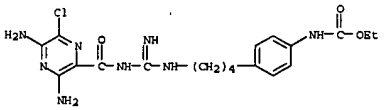
RN 587879-95-6 CAPLUS
CN Pyrazinecarboxamide, N-[[[4-[4-(acetylamino)phenyl]butyl]amino]iminomethyl]-3,5-diamino-6-chloro- (9CI) (CA INDEX NAME)



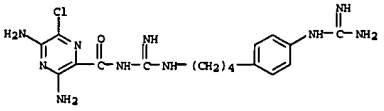
RN 587879-96-7 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[4-[4-[(methylsulfonyl)amino]phenyl]butyl]amino]methyl]-(9CI) (CA INDEX NAME)



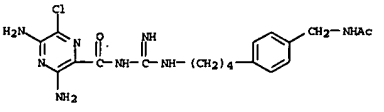
RN 587879-97-8 CAPLUS
CN Carbamic acid, [4-[4-[[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenyl]-, ethyl ester (9CI) (CA INDEX NAME)



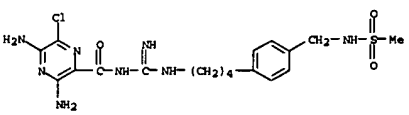
RN 587879-98-9 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[(aminoiminomethyl)amino]phenyl]butyl]amino]iminomethyl]-6-chloro-(9CI) (CA INDEX NAME)



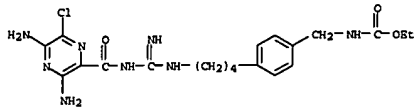
RN 587879-99-0 CAPLUS
CN Pyrazinecarboxamide, N-[[[4-[4-[(acetylamino)methyl]phenyl]butyl]amino]iminomethyl]-3,5-diamino-6-chloro- (9CI) (CA INDEX NAME)



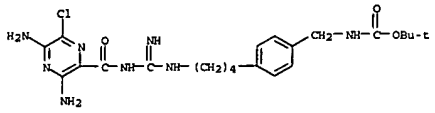
RN 587880-00-0 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[4-[4-[[(methylsulfonyl)amino]methyl]phenyl]butyl]amino]methyl]-(9CI) (CA INDEX NAME)



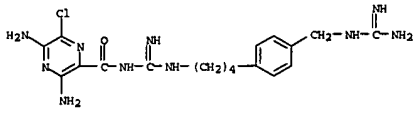
RN 587880-01-1 CAPLUS
CN Carbamic acid, [[4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenyl]methyl]-, ethyl ester (9CI) (CA INDEX NAME)



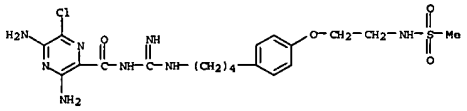
RN 587880-02-2 CAPLUS
CN Carbamic acid, [[4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenyl]methyl]-,1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



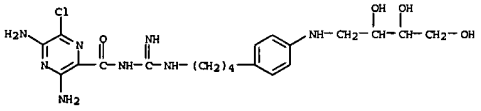
RN 587880-03-3 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[[(aminoiminomethyl)amino]methyl]phenyl]butyl]amino]iminomethyl]-6-chloro-(9CI) (CA INDEX NAME)



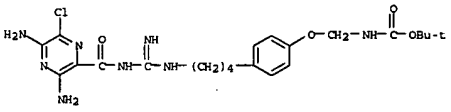
RN 587880-04-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[4-[4-[2-[(methylsulfonyl)amino]ethoxy]phenyl]butyl]amino]methyl]-(9CI) (CA INDEX NAME)



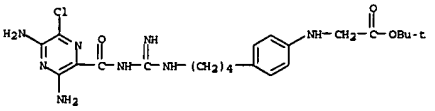
RN 587880-05-5 CAPLUS
CN Pyrazinecarboxamide, N-[[[4-[4-[2-(acetylamino)ethoxy]phenyl]butyl]amino]iminomethyl]-3,5-diamino-6-chloro-(9CI) (CA INDEX NAME)



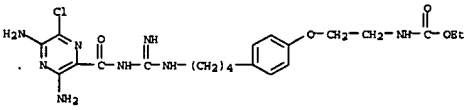
RN 587880-10-2 CAPLUS
CN Carbamic acid, [[4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenoxy]methyl]-,1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



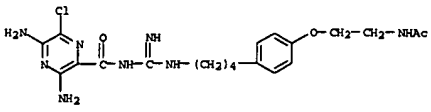
RN 587880-12-4 CAPLUS
CN Glycine, N-[4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



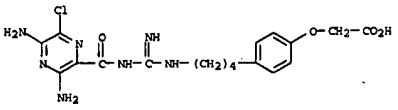
RN 587880-13-5 CAPLUS
CN Carbamic acid, [2-[4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenoxy]ethyl]-,ethyl ester (9CI) (CA INDEX NAME)



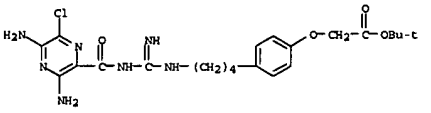
RN 587880-14-6 CAPLUS
CN Carbamic acid, [3-[4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenoxy]-2-hydroxypropyl]-,1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



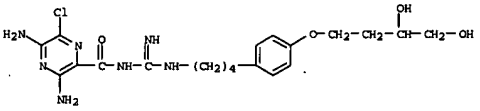
RN 587880-06-6 CAPLUS
CN Acetic acid, [4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenoxy]-(9CI) (CA INDEX NAME)



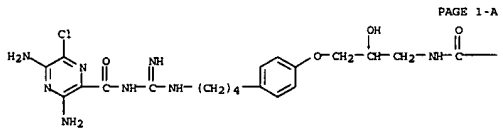
RN 587880-07-7 CAPLUS
CN Acetic acid, [4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenoxy]-,1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



RN 587880-08-8 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-(3,4-dihydroxybutoxy)phenyl]butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



RN 587880-09-9 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[4-[4-[(2,3,4-trihydroxybutyl)amino]phenyl]butyl]amino]methyl]-(9CI) (CA INDEX NAME)

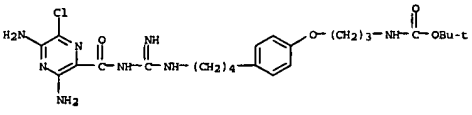


PAGE 1-A

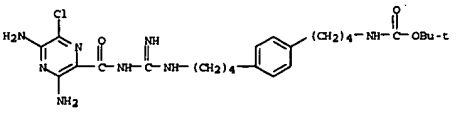
PAGE 1-B

—OBu-t

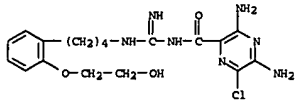
RN 587880-15-7 CAPLUS
CN Carbamic acid, [3-[4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenoxy]propyl]-,1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



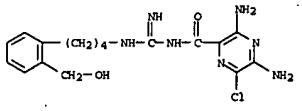
RN 587880-16-8 CAPLUS
CN Carbamic acid, [4-[4-[4-[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenyl]butyl]-,1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



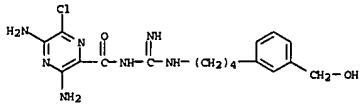
RN 587880-17-9 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[2-(2-hydroxyethoxy)phenyl]butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



RN 587880-18-0 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[2-(hydroxymethyl)phenyl]butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



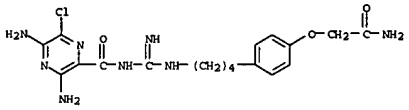
RN 587880-19-1 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[3-(hydroxymethyl)phenyl]butyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



RN 587880-20-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-(2-amino-2-oxoethoxy)phenyl]butyl]amino]iminomethyl]-6-chloro-,monomethanesulfonate (9CI) (CA INDEX NAME)

CM 1

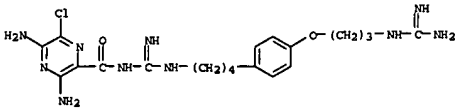
CRN 587879-43-4
CMF C18 H23 Cl N8 O3



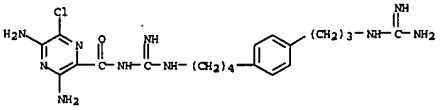
CM 2

CRN 75-75-2
CMF C H4 O3 S

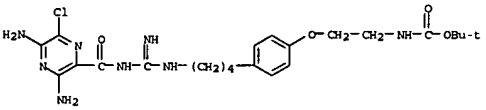
RN 587880-21-5 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[3-[(aminoiminomethyl)amino]propoxy]phenyl]butyl]amino]iminomethyl]-6-chloro-(9CI) (CA INDEX NAME)



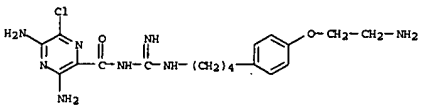
RN 587880-22-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[3-[(aminoiminomethyl)amino]propyl]phenyl]butyl]amino]iminomethyl]-6-chloro-(9CI) (CA INDEX NAME)



RN 587880-56-6 CAPLUS
CN Carbamic acid, [2-[4-[4-[[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenoxy]ethyl]-,1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

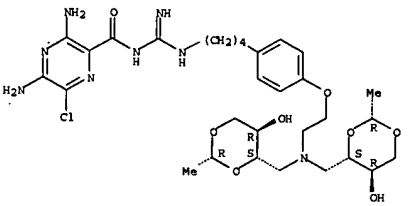


RN 587880-57-7 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-(2-aminoethoxy)phenyl]butyl]amino]iminomethyl]-6-chloro-(9CI) (CA INDEX NAME)

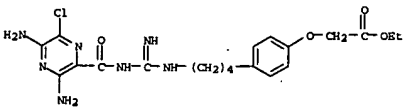


RN 587880-62-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[4-[4-[2-[bis[[(2R,4S,5R)-5-hydroxy-2-methyl-1,3-dioxan-4-yl]methyl]amino]ethoxy]phenyl]butyl]amino]iminomethyl]-6-chloro- (9CI) (CA INDEX NAME)

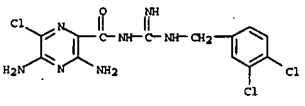
Absolute stereochemistry. Rotation (-).



RN 587880-76-0 CAPLUS
CN Acetic acid, [4-[4-[[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]butyl]phenoxy]-, ethyl ester (9CI) (CA INDEX NAME)



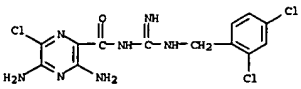
L6 ANSWER 19 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:649816 CAPLUS
DOCUMENT NUMBER: 140:87355
TITLE: Effects of dichlorobenzamil upon the contractile activity of isolated rat aorta
AUTHOR(S): Serban, I. L.; Serban, D. N.; Slatineanu, S. M.; Petrescu, G.
CORPORATE SOURCE: Department of Physiology, University of Medicine and Pharmacy "Gr. T. Popa", Iasi, Rom.
SOURCE: Microcirculation and Vascular Biology, Meeting of the European Society for Microcirculation, 22nd, Exeter, United Kingdom, Aug. 28-30, 2002 (2002), 263-266. Editor(s): Tooke, John; Shore, Angela; Whatmore, Jacqueline. Monduzzi Editore: Bologna, Italy. CODEN: 69EIUX; ISBN: 88-323-2828-3
DOCUMENT TYPE: Conference
LANGUAGE: English
AB We studied the effects of amiloride derivative dichlorobenzamil (DCB) upon contractile activity of isolated rat aorta rings. The results are expressed as % active tension of reference contractions induced either by 40 mM K+ or by 10-5 M phenylephrine (PHE) in the same preparation. High K+-precontracted rings are partially relaxed by at least 10-4 M DCB, while PCB pretreatment is somewhat stronger. DCB abolishes PHE-induced contractions in both pre- and post-treatment protocols. With both agents DCB alters the contraction time course, with a decreased contribution of the fast initial phase and an increase in the time to plateau. DCB preferentially inhibits contraction induced by the a1 adrenoceptor agonist vs. that induced by high K+ and the development vs. the maintenance of active force. Given the known roles of sodium-calcium exchange in smooth muscle, it is unlikely that these effects involve its inhibition.
IT 1166-01-4, Dichlorobenzamil
RL: PAC (Pharmacological activity); BIOL (Biological study)
(effects of dichlorobenzamil upon the contractile activity of isolated rat aorta)
RN 1166-01-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 20 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:567519 CAPLUS
DOCUMENT NUMBER: 139:391466
TITLE: Spermicidal efficacy of H2-receptor antagonists and potentiation with 2',4'-dichlorobenzamil hydrochloride: role of intrasperm Ca2+
AUTHOR(S): Gupta, A.; Gupta, S.; Tiwary, A. K.
CORPORATE SOURCE: Department of Pharmaceutical Sciences and Drug Research, Punjabi University, Patiala, 147 002, India
SOURCE: Contraception (2003), 68(1), 61-64
CODEN: CCPTAY; ISSN: 0010-7824
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The present investigation was designed to study the possible role of intrasperm Ca2+ in spermicidal action of H2-receptor antagonists. Influence of commonly used H2-receptor antagonists cimetidine, ranitidine and famotidine on sperm viability and intrasperm Ca2+ was evaluated in ejaculated human semen samples. All these drugs were found to reduce sperm viability in a dose- and time-dependent manner. This action was accompanied with elevation of intrasperm Ca2+. 2',4'-Dichlorobenzamil hydrochloride (DBZ), a Na-Ca exchange inhibitor, that is known to elevate intrasperm Ca2+, potentiated the spermicidal action of H2-receptor antagonists. Intrasperm Ca2+ was found to rise at much faster rate when DBZ was combined with any of the three H2-receptor antagonists. Due to this, the maximum Ca2+ level required to produce death of sperm cells was attained much earlier as compared to the per se effect of any one of these drugs. These results suggest that elevation of intrasperm Ca2+ by H2-receptor antagonists plays a key role in influencing sperm viability.

IT 2088-58-6, 2',4'-Dichlorobenzamil hydrochloride
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(spermicidal efficacy of H2-receptor antagonists and potentiation with dichlorobenzamil-HCl and role of intrasperm calcium)
RN 2088-58-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2,4-dichlorophenyl)methyl]amino]iminomethyl]-,monohydrochloride (9CI) (CA INDEX NAME)



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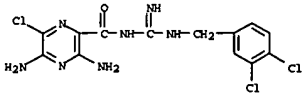
REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

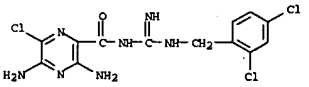
L6 ANSWER 21 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:60171 CAPLUS
DOCUMENT NUMBER: 139:257355
TITLE: Effects of extracellular Na+ and Ca2+ ions and Ca2+ channel modulators on the cell-associated activity of 99mTc-MIBI and 99mTc-tetrofosmin in tumour cells
AUTHOR(S): Arbab, A. S.; Ueki, J.; Koizumi, K.; Araki, T.
CORPORATE SOURCE: Department of Radiology, Yamanashi Medical University, Yamanashi, Japan
SOURCE: Nuclear Medicine Communications (2003), 24(2), 155-166
CODEN: NMCODC; ISSN: 0143-3636
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Our aim was to determine whether the Ca2+ ion or cell membrane Ca2+ and Na+/Ca2+ ion transport systems are involved in maintaining the cell-associated activity of technetium-99m-hexakis-methoxy-isobutyl-isonitrile (99mTc-MIBI) and technetium-99m-ethylene-bis[bis(2-ethoxyethyl)phosphin] (99mTc-tetrofosmin) in tumor cell lines. The cell-associated activities of 99mTc-MIBI and 99mTc-tetrofosmin were assessed in various buffers, with or without Na and/or with different concns. of Ca2+, in Lewi's murine lung cell carcinoma and human glioma cell lines. Different Ca channel modulators, such as verapamil, flunarizine and 3,4-dichlorobenzamil (DCB), were used to assess the effect of Ca channels on the cell-associated activity of 99mTc-MIBI and 99mTc-tetrofosmin. Despite significant differences between cell lines, the cell-associated activity of 99mTc-MIBI was higher in buffers without extracellular Ca2+ and Na+. The cell-associated activity of 99mTc-MIBI was significantly lower in all buffers containing high concns. of Ca2+ in both cell lines. The cell-associated activity
of 99mTc-tetrofosmin was also significantly higher in buffers without Ca2+, and was significantly decreased in buffers with high concns. of Ca2+. All modulators significantly increased the cell-associated activity of 99mTc-MIBI in both cell lines in all buffers. All modulators increased the cell-associated activity of 99mTc-tetrofosmin, particularly in buffers containing Ca2+. The cell-associated activities of both 99mTc-MIBI and 99mTc-tetrofosmin may be dependent on verapamil-, flunarizine- and DCB-sensitive Ca2+ channels.

IT 1166-01-4, Dichlorobenzamil
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(extracellular Na+ and Ca2+ ions and verapamil-, flunarizine- and DCB-sensitive Ca2+ channels modulation of tumor cell-associated activity of 99mTc-MIBI and 99mTc-tetrofosmin)
RN 1166-01-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



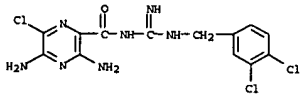
REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 22 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:2276 CAPLUS
DOCUMENT NUMBER: 138:231884
TITLE: Potentiation of spermicidal activity of 2',4'-dichlorobenzamil by lidocaine
AUTHOR(S): Moudgil, P.; Gupta, A.; Sharma, A.; Gupta, S.; Tiwary, A. K.
CORPORATE SOURCE: Department of Pharmaceutical Sciences and Drug Research, Punjab University, Patiala, 147 002, India
SOURCE: Indian Journal of Experimental Biology (2002), 40(12), 1373-1377
CODEN: IJEBA6; ISSN: 0019-5189
PUBLISHER: National Institute of Science Communication
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The present investigation was designed to study the spermicidal activity of lidocaine, a membrane stabilizer, and its combination with 2',4'-dichlorobenzamil hydrochloride, a Na+-Ca2+ exchange inhibitor, on human semen and spermatozoa separated from semen. Both drugs per se produced dose- and time-dependent reduction in motility of ejaculated human sperm. Lidocaine was found to potentiate the spermicidal activity of benzamil resulting in significant decrease in time for producing complete loss of ejaculated sperm motility. Sperm revival test revealed irreversible loss of sperm viability indicating a spermicidal rather than spermiostatic action by both the drugs. Furthermore, both benzamil (10-40 mM) per se and benzamil-lidocaine combination (0.5 and 16 mM) produced contraception in rabbit model.
IT 90689-42-2, 2',4'-Dichlorobenzamil
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(lidocaine potentiation of spermicidal activity of benzamil)
RN 90689-42-2 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)

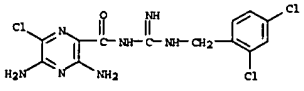


REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

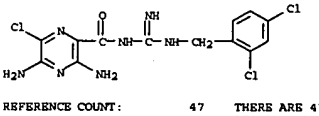
L6 ANSWER 23 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:336733 CAPLUS
DOCUMENT NUMBER: 139:143314
TITLE: Novel inhibitors of the sodium-calcium exchanger: benzene ring analogues of N-guanidino substituted amiloride derivatives. [Erratum to document cited in CA136:272643]
AUTHOR(S): Rogister, Francoise; Laeckmann, Didier; Plasman, Pierre-Olivier; Van Eylen, Francoise; Ghyoot, Marianne; Maggetto, Carine; Sokolow, Sophie; Liegeois, Jean-Francois; Geczy, Joseph; Masereel, Bernard; Delarge, Jacques; Herchuelz, Andre
CORPORATE SOURCE: Laboratory of Medicinal Chemistry, University of Liege, Liege, B-4000, Belg.
SOURCE: European Journal of Medicinal Chemistry (2002), 37(5), 441
CODEN: EJMCA5; ISSN: 0223-5234
PUBLISHER: Editions Scientifiques et Medicales Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The name of co-author Sophie Sokolow is added and the corrected author list is given.
IT 1166-01-4 90689-42-2
RL: PAC (Pharmacological activity); BIOL (Biological study)
(benzene ring analogs of N-guanidino substituted amiloride derivs. as novel inhibitors of sodium-calcium exchanger in relation to structure (Erratum))
RN 1166-01-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



RN 90689-42-2 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



L6 ANSWER 24 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:917 CAPLUS
DOCUMENT NUMBER: 137:44582
TITLE: Characterization of the Drosophila melanogaster alkali-metal/proton exchanger (NHE) gene family
AUTHOR(S): Giannakou, Maria E.; Dow, Julian A. T.
CORPORATE SOURCE: Division of Molecular Genetics, Institute of Biomedical and Life Sciences, University of Glasgow, Glasgow, G11 6NU, UK
SOURCE: Journal of Experimental Biology (2001), 204(21), 3703-3716
CODEN: JEBIAM; ISSN: 0022-0949
PUBLISHER: Company of Biologists Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The NHE family of Na+/H+ exchangers is believed to play an essential role in animals, but may play an addnl., specialized epithelial role in insects. The pharmacol. sensitivity of the Drosophila melanogaster Malpighian tubule to a range of amiloride derivs. was shown to be consistent with an effect on an exchanger, rather than a Na+ channel. Consistent with this, no degenerin/epithelial Na+ channel (ENaC) genes could be detected in Malpighian tubules by reverse transcriptase/polymerase chain reaction (RT-PCR). Using a low-stringency homol. searching, three members of the NHE family were identified in the genomic sequence of Drosophila melanogaster, although only two genes were represented as expressed sequence tags. All three genes (DmNHE1 at cytol. position 21B1, DmNHE2 at 39B1 and DmNHE3 at 27A1) were found by RT-PCR to be widely expressed, and one (DmNHE2) was shown to have multiple transcripts. The putative translations of the three genes mark them as distantly related members of the family, inviting the possibility that they may serve distinct roles in insects.
IT 90689-42-2, 2',4'-Dichlorobenzamil
RL: ADV (Adverse effect, including toxicity); ARG (Analytical reagent use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(alkali-metal/proton exchanger (NHE) gene family characterization in Drosophila melanogaster)
RN 90689-42-2 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

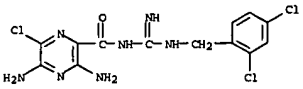
L6 ANSWER 25 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:861867 CAPLUS
DOCUMENT NUMBER: 136:128821
TITLE: Amiloride derivatives are potent blockers of KATP channels
AUTHOR(S): Bollensdorff, Christian; Zimmer, Thomas; Benndorf, Klaus
CORPORATE SOURCE: Institut fur Physiologie, Abteilung Herz-Kreislauf-Physiologie, Friedrich-Schiller-Universitat Jena, Jena, 07740, Germany
SOURCE: Naunyn-Schmiedeberg's Archives of Pharmacology (2001), 364(4), 351-358
CODEN: NSAPCC; ISSN: 0028-1298
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The diuretic drug amiloride and related derivs. are well established as drugs blocking the Na+/H+ and the Na+/Ca2+ exchange, protecting the ischemic heart. The blocking action of amiloride and its deriv.

2',4'-dichlorobenzamil (DCB) and 5-(N-ethyl-N-isopropyl)amiloride(EIPA) on KATP channels was tested. In inside-out patches of mouse cardiac myocytes, amilorido, DCB, and EIPA reversibly blocked the KATP channels, with IC50 values of 102, 1.80, and 2.14 μM (-80 mV), resp. Similar IC50 values were obtained in recombinant channels coexpressing the KIR6.2 subunit with one of the sulfonylurea receptors SUR1 and SUR2A. All three drugs also blocked currents generated by the C-terminus deletion mutant KIR6.2Δ26 in the absence of SUR. Amiloride blocked outward currents ' more effectively than inward currents, whereas the block by DCB and EIPA was voltage independent. In cardiomyocytes, whole-cell IKATP was also blocked by the three drugs. In conclusion, amiloride, EIPA, and DCB block the pore-forming KIR6.2 subunit of cardiac KATP channels with higher potency than the Na+/H+ and the Na+/Ca2+ exchange, precluding a specific block of the exchanges under ischemic conditions.

IT 90689-42-2, 2',4'-Dichlorobenzamil
RL: PAC (Pharmacological activity); BIOL (Biological study)
(blockade of cardiac KATP channels by amiloride and derivs.)

RN 90689-42-2 CAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 26 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2001:849153 CAPLUS

DOCUMENT NUMBER: 136:79942

TITLE: Role of intracellular calcium in the spermicidal action of 2',4'-dichlorobenzamil, a novel contact spermicide

AUTHOR(S): Patni, Anil K.; Gupta, Sunil; Sharma, Ajay; Tiwary, Ashok K.; Garg, Santosh K.

CORPORATE SOURCE: Department of Pharmaceutical Sciences & Drug Research, Punjabi University, Patiala, 147 002, India

SOURCE: Journal of Pharmacy and Pharmacology (2001), 53(10), 1387-1392
CODEN: JPPMAB; ISSN: 0022-3573

PUBLISHER: Pharmaceutical Press

DOCUMENT TYPE: Journal

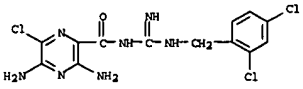
LANGUAGE: English

AB The Na+-Ca2+ exchanger and Ca2+-ATPase pumps reported to be present on the sperm membrane are responsible for maintaining the intracellular Ca2+ concentration that is involved in regulation of sperm function. The authors have investigated the role of intracellular Ca2+ in the presence of 2',4'-dichlorobenzamil hydrochloride (benzamil), a Na+-Ca2+ exchange inhibitor, on human sperm motility. The mechanism of the complementary spermicidal action produced by a combination of benzamil and propranolol on human spermatozoa has been investigated also. When administered alone benzamil and propranolol produced a dose- and time-dependent decrease in motility of sperm in ejaculated semen and spermatozoa separated from semen. A combination of benzamil and propranolol exhibited a complementary spermicidal action, thereby resulting in dose reduction of both drugs for obtaining total immotility within 1 min of administration. An increase in the intracellular Ca2+ level was found to contribute to the spermicidal activity. Inhibition of the Na+-Ca2+ exchange system on sperm membrane by benzamil and membrane stabilization by propranolol resulted in accumulation of Ca2+ inside the sperm cells. When the two drugs were used in combination the time required for the total loss of motility of spermatozoa was significantly reduced due to a similar mechanism of action of both drugs.

IT 90689-42-2, 2',4'-Dichlorobenzamil
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(intracellular calcium in mechanism of spermicidal action of dichlorobenzamil contact spermicide in human)

RN 90689-42-2 CAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 27 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2001:746737 CAPLUS

DOCUMENT NUMBER: 136:272643

TITLE: Novel inhibitors of the sodium-calcium exchanger: benzene ring analogues of N-guanidino substituted amiloride derivatives

AUTHOR(S): Register, P.; Leeckmann, D.; Plasman, P.-O.; Van Bylen, F.; Ghyoot, M.; Maggetto, C.; Liegeois, J.-F.; Geczy, J.; Herchuelz, A.; Delarge, J.; Masereel, B.

CORPORATE SOURCE: Laboratory of Medicinal Chemistry, University of Liege, Liege, B-4000, Belg.

SOURCE: European Journal of Medicinal Chemistry (2001), 36(7-8), 597-614
CODEN: EJMCA5; ISSN: 0223-5234

PUBLISHER: Editions Scientifiques et Medicales Elsevier

DOCUMENT TYPE: Journal

LANGUAGE: English

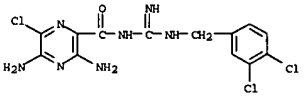
OTHER SOURCE(S): CASREACT 136:272643

AB A series of N-guanidino substituted 2,4-diamino-5-carbonylguanidinemols. related to amiloride were synthesized and evaluated for their ability to inhibit the sodium-calcium exchanger in rat insulinoma cells (RINm5F) and human platelets. Specific chemical pathways were used to prepare the benzene deriv. designed as bioisosteric analogs of the pyrazine derivs. of amiloride. Several so-called 'simplified analogs', where some substituents of amiloride were omitted or replaced, were also prepared and included in the biol. evaluation. The inhibitory potency of the sodium-calcium exchanger was screened on both cell types by measuring their effect on 45Ca2+ uptake. Among the most active compds., N-(2-amino-5-chloro-4-nitrobenzoyl)-N'-(1-naphthylmethyl)guanidine (IC50=3.4 μM) was found more active than amiloride (IC50=690 μM) and 3,4-dichlorobenzamil (IC50=15.2 μM), the reference inhibitor.

IT 1166-01-4 90689-42-2
RL: PAC (Pharmacological activity); BIOL (Biological study)
(benzene ring analogs of N-guanidino substituted amiloride derivs. as novel inhibitors of sodium-calcium exchanger in relation to structure)

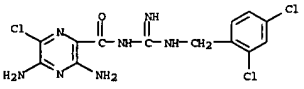
RN 1166-01-4 CAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



RN 90689-42-2 CAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



REFERENCE COUNT: 68 THERE ARE 68 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 28 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2001:599395 CAPLUS

DOCUMENT NUMBER: 135:316398

TITLE: The mechanism of phenylephrine-mediated [Ca2+]i oscillations underlying tonic contraction in the rabbit inferior vena cava

AUTHOR(S): Lee, Cheng-Han; Poburko, Damon; Sahota, Paul; Sandhu, Jasmin; Ruehlmann, Dietrich O.; Van Breemen, Cornelis

CORPORATE SOURCE: Vancouver Vascular Biology Research Center, St Paul's Hospital, University of British Columbia, Vancouver, BC, V6Z 1Y6, Can.

SOURCE: Journal of Physiology (Cambridge, United Kingdom) (2001), 534(3), 641-650
CODEN: JPHYA7; ISSN: 0022-3751

PUBLISHER: Cambridge University Press

DOCUMENT TYPE: Journal

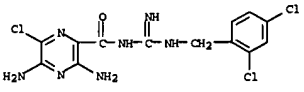
LANGUAGE: English

AB The authors characterized the mechanisms in vascular smooth muscle cells (VSMCs) that produce asynchronous, wave-like Ca2+ oscillations in response to phenylephrine (PE). Confocal imaging was used to observe [Ca2+]i in individual VSMCs of intact inferior vena cava (IVC) from rabbits. It was found that the Ca2+ waves were initiated by Ca2+ release from the sarcoplasmic reticulum (SR) via inositol 1,4,5-trisphosphate-sensitive SR Ca2+ release channels (IP3R channels) and that refilling of the SR Ca2+ store through the sarcoplasmic-endoplasmic reticulum Ca2+-ATPase (SERCA) was required for maintained generation of the repetitive Ca2+ waves. Blockade of L-type voltage-gated Ca2+ channels (L-type VGCCs) with nifedipine reduced the frequency of PE-stimulated [Ca2+]i oscillations, while addnl. blockade of receptor-operated channels/store-operated channels (ROCs/SOCs) with SKF96365 abolished the remaining oscillations. Parallel force measurements showed that nifedipine inhibited PE-induced tonic contraction by 27% while SKF96365 abolished it. This indicates that stimulated Ca2+ entry refills the SR to support the recurrent waves of SR Ca2+ release and that both L-type VGCCs and ROCs/SOCs contribute to this process. Application of the Na+-Ca2+ exchanger (NCX) inhibitors 2',4'-dichlorobenzamil (forward- and reverse-mode inhibitor) and KB-R7943 (reverse-mode inhibitor) completely abolished the nifedipine-resistant component of [Ca2+]i oscillations and markedly reduced PE-induced tone. Thus, the authors conclude that each Ca2+ wave depends on initial SR Ca2+ release via IP3R channels followed by SR Ca2+ refilling through SERCA. Na+ entry through ROCs/SOCs facilitates Ca2+ entry through the NCX operating in the reverse mode, which refills the SR and maintains PE-induced [Ca2+]i oscillations. In addition some Ca2+ entry through L-type VGCCs and ROCs/SOCs serves to modulate the frequency of the oscillations and the magnitude of force development.

IT 90689-42-2, 2',4'-Dichlorobenzamil
RL: ARG (Analytical reagent use); BPR (Biological process); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study); PROC (Process); USES (Uses)
(Na+-Ca2+ exchanger (NCX) inhibitor; phenylephrine-mediated calcium [Ca2+]i oscillations underlying tonic contraction in the rabbit inferior vena cava and mechanisms)

RN 90689-42-2 CAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 29 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2001:429969 CAPLUS

DOCUMENT NUMBER: 135:267056

TITLE: Inhibitors of Na+/H+ and Na+/Ca2+ exchange potentiate methamphetamine-induced dopamine neurotoxicity: possible role of ionic dysregulation in methamphetamine neurotoxicity

AUTHOR(S): Callahan, Brian T.; Cord, Branden J.; Yuan, Jie; McCann, Una D.; Ricaurte, George A.

CORPORATE SOURCE: Department of Neurology and Psychiatry, Johns Hopkins Medical Institutions, Baltimore, MD, 21224, USA

SOURCE: Journal of Neurochemistry (2001), 77(5), 1348-1361
CODEN: JONRA9; ISSN: 0022-3042

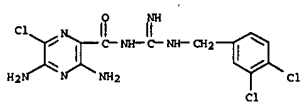
PUBLISHER: Blackwell Science Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

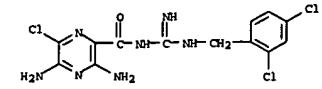
AB Although the neurotoxic potential of methamphetamine (METH) is well established, underlying mechanisms have yet to be identified. In the present study, we sought to determine whether ionic dysregulation was a feature of METH neurotoxicity. In particular, we reasoned that if METH impairs the function of Na+/H+ and/or Na+/Ca2+ antiporters by compromising the inward Na+ gradient [via prolonged DA transporter (DAT) activation and Na+/K+ ATPase inhibition], then amiloride (AMIL) and other inhibitors of Na+/H+ and/or Na+/Ca2+ exchange would potentiate METH neurotoxicity. To test this hypothesis, mice were treated with METH alone or in combination with AMIL or one of its analogs; 1 wk later, the animals were killed for studies of dopamine (DA) neuronal integrity. AMIL markedly potentiated the toxic effect of METH on DA neurons. Potentiation was not caused by increased core temperature, enhanced DAT activity or higher METH brain levels. The DAT inhibitor, WIN-35,428, protected completely against METH-induced DA neurotoxicity in AMIL pretreated animals, suggesting that the potentiating effects of AMIL require a METH/DAT interaction. Findings with METH and AMIL were extended to six other AMIL analogs (MIA, EIPA, DIMA, BENZ, BEP, DiCBNZ), another species (rats), and neuronal type (5-HT neurons). These results support the notion that ionic dysregulation may play a role in METH neurotoxicity.

IT 1166-01-4, Dichlorobenzamil
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors of Na+/H+ and Na+/Ca2+ exchangers potentiate methamphetamine-induced dopamine neurotoxicity)
RN 1166-01-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



REFERENCE COUNT: 82 THERE ARE 82 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 30 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:315479 CAPLUS
DOCUMENT NUMBER: 135:131964
TITLE: Effect of 2',4'-dichlorobenzamil hydrochloride, a Na+-Ca2+ exchange inhibitor, on human spermatozoa
AUTHOR(S): Reddy, P. R.; Patni, A.; Sharma, A.; Gupta, S.; Tiwary, A. K.
CORPORATE SOURCE: Department of Pharmaceutical Sciences and Drug Research, Punjabi University, Patiala, 147 002, India
SOURCE: European Journal of Pharmacology (2001), 418(1,2), 153-155
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGES: English
AB The contact spermicidal efficacy of 2',4'-dichlorobenzamil hydrochloride (DBZ), a Na+-Ca2+ exchange inhibitor, on ejaculated human spermatozoa was investigated. The drug produced a dose- and time-dependent spermicidal action on human spermatozoa. A concentration of 4 mM produced total loss of sperm viability within 1 min of addition to total semen. On the other hand, a similar action on spermatozoa separated from semen was noted at 0.5 mM concentration The loss of spermatozoal viability was accompanied with an increase in intracellular Ca2+. Sperm revival testing with glucose suggested a spermicidal rather than a spermiostatic action.
IT 2088-58-6
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(human spermatozoa response to)
RN 2088-58-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2,4-dichlorophenyl)methyl]amino]iminomethyl]-,monohydrochloride (9CI) (CA INDEX NAME)



● HCl

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 31 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:63982 CAPLUS
DOCUMENT NUMBER: 134:115971
TITLE: Pyrazinoylguanidine derivatives as conjugates of sodium channel blockers and methods of using the same for hydrating mucosal surfaces
INVENTOR(S): Boucher, Richard C., Jr.
PATENT ASSIGNEE(S): University of North Carolina At Chapel Hill, USA
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001005773	A1	20010125	WO 2000-US19775	20000719
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2378181	A1	20010125	CA 2000-2378181	20000719
EP 1196396	A1	20020417	EP 2000-948820	20000719
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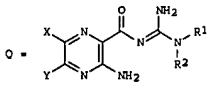
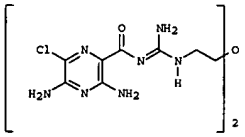
US 6475509	B1	20021105	US 2000-618978	20000719
NZ 516595	A	20030725	NZ 2000-516595	20000719
JP 2004513870	T	20040513	JP 2001-511434	20000719
AU 774865	B2	20040708	AU 2000-62262	20000719
ZA 2002000129	A	20030407	ZA 2002-129	20020107
NO 2002000242	A	20020319	NO 2002-242	20020116
US 2002165239	A1	20021107	US 2002-121913	20020412
US 6607741	B2	20030819		
US 6613345	B2	20030902	US 2002-121917	20020412
US 2002158255	A1	20030902		

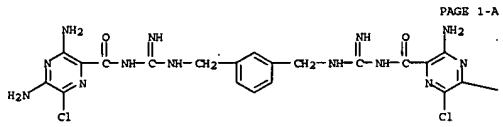
PRIORITY APPLN. INFO.:	US 1999-144479P	P	19990719
	US 2000-618978	A	20000719
	WO 2000-US19775	W	20000719

OTHER SOURCE(S): MARPAT 134:115971
GI





AB Compds. of the general formula P1-L-P2 [L = linker; P1 = a pyrazinoylguanidine sodium channel blocker; P2 = a dinucleotide, a pyrazinoylguanidine sodium channel blocker and/or a P2Y2 receptor agonist; P1 and P2 may be independently Q wherein X = halo, alkyl, cycloalkyl, (un)substituted Ph, alkylthio, alkylsulfonyl, oxyalkylthio, oxyalkylsulfonyl, phenylalkylthio and phenylalkylsulfonyl; Y = OH, mercapto, alkyloxy, alkylthio, Cl, alkyl, cycloalkyl, Ph and amino derivs.; R1 and R2 are independently selected from H, alkyl, hydroxyalkyl, (un)substituted phenylalkyl, etc.; L = alkyl, hydroxyalkyl, (un)substituted arylalkyl, etc.] are prepared and disclosed as conjugates of sodium channel blockers. Thus, I was prepared via substitution reactions of N-Cbz-1-(3,5-diamino-6-chloropyrazinoyl)-2-methylpseudothiourea with 1,5-diamino-3-oxapentane. I possessed an IC50 value of 1275 nM in an assay for Na+ channel subunit expression in Xenopus oocytes, and was found to absorb into cells less rapidly than amiloride. Pharmaceutical formulations containing the disclosed compds. and methods of use thereof to hydrate mucosal surfaces such as airway mucosal surfaces are also disclosed.
IT 321554-70-5P 321554-73-8P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of pyrazinoylguanidine derivs. as conjugates of sodium channel blockers used for hydration of mucosal surfaces)
RN 321554-70-5 CAPLUS
CN Pyrazinecarboxamide, N,N'-[1,3-phenylenebis(methyleneiminocarbonimidoyl)]bis[3,5-diamino-6-chloro-, dihydrobromide (9CI) (CA INDEX NAME)

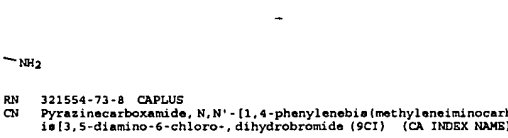


PAGE 1-A

PAGE 1-B

●2 HBr

RN 321554-73-8 CAPLUS
CN Pyrazinecarboxamide, N,N'-[1,4-phenylenebis(methyleneiminocarbonimidoyl)]bis[3,5-diamino-6-chloro-, dihydrobromide (9CI) (CA INDEX NAME)



PAGE 1-A

PAGE 1-B

●2 HBr

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

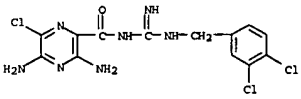
L6 ANSWER 32 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:172740 CAPLUS

DOCUMENT NUMBER: 132:329862
TITLE: Modulation of the Ca2+ release channel of sarcoplasmic reticulum by amiloride analogs
AUTHOR(S): Ponte, C. G.; Estrela, R. C. E.; Suarez-Kurtz, G.
CORPORATE SOURCE: Coordenacao de Pesquisa, Instituto Nacional de Cancer, Rio de Janeiro, Brazil
SOURCE: European Journal of Pharmacology (2000), 391(1/2), 11-20
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Dichlorobenzamil, phenamil and other amiloride analogs (1-100 μM) elicit transient tension in rabbit skinned muscle fibers. Tension requires preloading of Ca2+ into the sarcoplasmic reticulum, is facilitated by low-[Mg2+] solns., abolished by ruthenium red or by functional disruption of the sarcoplasmic reticulum, and is followed by inhibition of the caffeine-evoked tension. Bilayer recording of Cs+ currents through the sarcoplasmic reticulum Ca2+ release channel reveals that phenamil (10-100 μM) increases the open channel probability, whereas dichlorobenzamil affects the channel activity in a complex concentration-
and time-dependent manner: stimulation occurs throughout exposure to 10 μM, but is followed by channel blockade when 100 μM dichlorobenzamil is used. It is concluded that stimulation of the sarcoplasmic reticulum Ca2+ release channel accounts for the dichlorobenzamil- or phenamil-induced tension in skinned fibers, whereas depletion of sarcoplasmic reticulum Ca2+ stores and channel block (with dichlorobenzamil) explains the inhibition of the caffeine-evoked tension by amiloride analogs.

IT 1166-01-4, Dichlorobenzamil
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(modulation of Ca2+ release channel of sarcoplasmic reticulum by amiloride analogs)

RN 1166-01-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



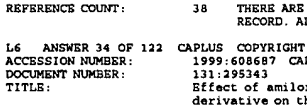
REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 33 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:147129 CAPLUS
DOCUMENT NUMBER: 132:274116
TITLE: Comparison of the protective actions of Na+/H+ and Na+/Ca2+ exchange inhibitors in ischemic/reperfused rat hearts
AUTHOR(S): Tachibana, Hiroko; Kitano, Yoshinori; Ishii, Mitsuo; Ninomiya, Mitsuyoshi; Iwaki, Kazumi
CORPORATE SOURCE: Discovery Research Laboratories, Shionogi and Co., Ltd, Osaka, 553-0002, Japan
SOURCE: Drug Development Research (1999), 48(4), 160-170
CODEN: DDRESK; ISSN: 0272-4391
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The protective effects of the Na+/H+ exchange inhibitors amiloride, EIPA (5-(N-ethyl-N-isopropyl)-amiloride),and HOE 694 (3-methylsulfonyl-4-(1-piperidino) benzoyl-guanidine) and the Na+/Ca2+ exchange inhibitor, DCB (3,4-Dichlorobenzamil) on ischemia (30 min) /reperfusion (30 min) injury were studied using Langendorff perfused rat hearts. EIPA and HOE 694 given before ischemia protected the heart during reperfusion from mech. and metabolic disturbances. A weak protective effect was observed with amiloride, but not with DCB. The cardioprotective efficacies of these compds. correlated with their potencies as Na+/H+ exchange inhibitors as assessed by the NH4Cl prepulse method. None of the inhibitors was effective when given at reperfusion. EIPA and HOE 694 decreased myocardial rigidity as assessed by the resting tension (RT) which elevated during reperfusion. EIPA led to a more marked attenuation of RT elevation during reperfusion rather than ischemia, whereas diltiazem, a Ca2+ channel blocker, suppressed RT elevation during ischemia but did not cause a further attenuation of RT during reperfusion. Treatment with EIPA as well as diltiazem before ischemia showed a direct neg. chronotropic effect. Cardioprotective effects were also observed with diltiazem. These results suggest that Na+/H+ exchange plays a more important role in ischemia-reperfusion-inducedmyocardial injury than does Na+/Ca2+ exchange. The cardioprotective effects of EIPA appear to be produced by Ca2+ channel blockade during ischemia and by Na+/H+ exchange inhibition during reperfusion.

IT 1166-01-4, Dichlorobenzamil
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(protective actions of Na+/H+ and Na+/Ca2+ exchange inhibitors in ischemic/reperfused hearts)

RN 1166-01-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



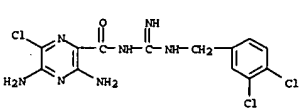
REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 34 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:608687 CAPLUS
DOCUMENT NUMBER: 131:295343
TITLE: Effect of amiloride and its dichlorobenzamil derivative on the isolated guinea pig atrium: interaction with other inotropic mechanisms
AUTHOR(S): Padron-Nieves, M.; Alfonso, C.; Lamanna, V.; Perez-Gonzalez, M.
CORPORATE SOURCE: Escuela Experimental de Enfermeria. Facultad de Medicina. Seccion de Investigaciones Cardio-Renales. Instituto de Medicina Experimental. Universidad Central de Venezuela, Venez.
SOURCE: Acta Cientifica Venezolana (1999), 50(1), 48-58
CODEN: ACVEAV; ISSN: 0001-5504
PUBLISHER: Asociacion Venezolana para el Avance de la Ciencia
DOCUMENT TYPE: Journal
LANGUAGE: Spanish

AB The inotropic and chronotropic effects of amiloride and dichlorobenzamil amiloride (I) were studied on the guinea pig isolated atrium, along with the interaction between these drugs and β-methyldigoxin, epinephrine, and low extracellular K+ (1 mM). Amiloride (10-3 M) had neg. chronotropic and pos. inotropic effects, which were not dependent on the autonomic system. I had a bimodal effect on the contractile force, increasing it at low concns. but decreasing it at concns. >10-6 M. The effect of amiloride on the sinus frequency was unchanged by β-methyldigoxin. Amiloride (10-3 M) decreased the inotropic effect of β-methyldigoxin and increase the toxic concentration of β-methyldigoxin in isolated tissues. The dose-response curve to epinephrine was not changed by amiloride. Similar results were obtained using I (2 × 10-7M). The pos. inotropic effect obtained by low extracellular K+ (1 mM) was not altered by amiloride. The activity of the Mg2+-dependent Na+/K+ ATPase measured in the microsomal fraction obtained from guinea pig heart was diminished 10% by amiloride (10-3 M). The drug did not affect the inhibition of the enzyme induced by ouabain. The results show multiple effects of amiloride and I on the guinea pig heart. The inhibition of the Na+/Ca2+ exchange explains them only partially. A slow channel blocking effect appears fundamental to interpret the results.

IT 1166-01-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effect of amiloride and its dichlorobenzamil derivative on isolated guinea pig atrium: interaction with other inotropic mechanisms)

RN 1166-01-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



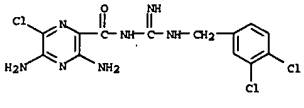
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 35 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:602844 CAPLUS
DOCUMENT NUMBER: 131:295337
TITLE: Effect of Na+/Ca2+ exchange inhibitor, KB-R7943 on ouabain-induced arrhythmias in guinea-pigs
AUTHOR(S): Watano, Tomokazu; Harada, Yoshimitsu; Harada, Kengo; Nishimura, Noriyasu
CORPORATE SOURCE: Department of Pharmacology, School of Medicine, Fukushima Medical University, Fukushima, 960-1295, Japan
SOURCE: British Journal of Pharmacology (1999), 127(8), 1846-1850
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Stockton Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We investigated protective effects of KB-R7943, a Na+/Ca2+ exchange (NCX) inhibitor, on ouabain-induced tonotropy and arrhythmias in isolated whole atria and ouabain-induced changes in ECG in the guinea-pig. KB-R7943 (10 and 30 μM) suppressed the tonotropic effect of ouabain, and prolonged the onset time of extra-systole induced by ouabain in isolated atria. The i.v. injection of KB-R7943 (1 and 3 mg kg-1) significantly increased the doses of ouabain required to induce ventricular premature beats (VPB), ventricular tachycardia (VT), ventricular fibrillation (VF) and cardiac arrest (CA) in anesthetized guinea-pigs. Lidocaine (Na+ channel inhibitor) and R56865 (Na+ and Ca2+ overload inhibitor) also suppressed the ouabain-induced tonotropic effect and extra-systole in isolated atria, but Hoe-694 (Na+/H+ exchange inhibitor) or diltiazem (Ca2+ channel inhibitor) did not affect them. Lidocaine also increased the doses of ouabain required to induce VPB, VT, VF and CA in anesthetized guinea-pigs. From these results, we conclude that KB-R7943 suppresses ouabain-induced arrhythmias through inhibition of the reverse-mode NCX.

IT 1166-01-4, 3',4'-Dichlorobenzamil
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(effect of KB-R7943 and other compds. on ouabain-induced arrhythmias)

RN 1166-01-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 36 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:441512 CAPLUS
DOCUMENT NUMBER: 131:193965
TITLE: Effect of amiloride analogs on DOCA-salt-induced hypertension in rats
AUTHOR(S): Keep, Richard F.; Si, Xiaochen; Shakui, Parvin; Ennis, Steven R.; Betz, A. Lorris
CORPORATE SOURCE: Dep. Surgery (Section of Neurosurgery), Univ. Michigan, Ann Arbor, MI, 48109-0532, USA
SOURCE: American Journal of Physiology (1999), 276(6, Pt. 2), H2215-H2220
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English

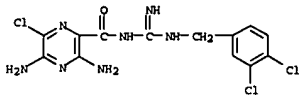
AB Intracerebroventricular infusions of an amiloride analog, benzamil, reduce blood pressure in several rat models of hypertension. This effect has been attributed to an inhibition of amiloride-sensitive Na+ channels in the brain. This study examines whether intracerebroventricular benzamil would prevent the onset of deoxycorticosterone acetate (DOCA)-salt-induced hypertension in rats and whether this effect correlates with an inhibition of ion transport through the known amiloride-sensitive cation channels at the blood-brain barrier. We also examine whether the effects of benzamil on blood pressure are mediated by a Na+ channel by comparing the effects of different amiloride analogs. Benzamil (0.15 and 0.5 μg/h icv) did significantly attenuate the increase in blood pressure induced by DOCA treatment. This antihypertensive effect, however, was not associated with an alteration in a blood-brain barrier ion transport as assessed by measurements of blood-to-brain 22Na transport and cerebral spinal fluid Na+ and K+ concns. Indeed, intracerebroventricular infusion of di-Me amiloride, an amiloride analog with low affinity for Na+ channels, also attenuated the increase in blood pressure induced by DOCA-salt treatment. Comparisons of the effects of benzamil, di-Me amiloride, and 3,4-dichlorobenzamil, another amiloride analog, suggest that these

antihypertensive effects are mediated by an inhibition of Na+/Ca2+ exchange in the brain.

IT 1166-01-4, Dichlorobenzamil
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effect of amiloride analogs on DOCA-salt-induced hypertension in rats in relation to blood-brain barrier ion transport)

RN 1166-01-4 CAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 37 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1998:757946 CAPLUS

DOCUMENT NUMBER: 130:119346

TITLE: Pharmacological tests of the mechanism of the periodic rhythm caused by veratramine in the sinoatrial node of the guinea pig

AUTHOR(S): Thron, C. D.; McCann, F. V.

CORPORATE SOURCE: DEPARTMENT OF PHARMACOLOGY, DARTMOUTH MEDICAL SCHOOL, HANOVER, NH, 03755-3835, USA

SOURCE: General Pharmacology (1998), Volume Date 1999, 32(1), 81-89
CODEN: GEPHDP; ISSN: 0306-3623

PUBLISHER: Elsevier Science Inc.

DOCUMENT TYPE: Journal

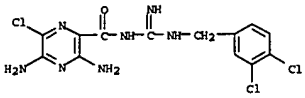
LANGUAGE: English

AB We investigated the effects of several drugs and extracellular ions on the periodic sinoatrial node rhythm caused by high concns. of veratramine (>2 μM) in isolated guinea pig sinus atria. During the active phase of this rhythm, pacemaker activity appeared to be due to transient after-depolarizations resembling the delayed afterdepolarizations attributed to Ca2+-induced Ca2+ release in cardiac tissue. Ryanodine (200-2200 nM) did not decrease the transient afterdepolarizations, and instead increased the heart rate during the active phase, prolonged the active phase, and sometimes caused conversion to regular rhythm. Dichlorobenzamil (10-110 μM), a blocker of electrogenic Na+-Ca2+ exchange, did not slow or stop beating during periodic rhythm, but rather increased average heart rate and, at a higher concentration, caused conversion to regular rhythm. Ouabain (0.1 μM), an inhibitor of the sodium pump and electrogenic Na+-K+ exchange, had little effect on veratramine periodic rhythm, but at higher concns. it caused increased average heart rate and conversion to regular rhythm. The chronotropic effect of Ca2+ was normally weakly pos.; however, in the presence of veratramine, and before the appearance of periodic rhythm, the chronotropic effect of Ca2+ was weakly neg., and was associated with destabilization of the heart rate, leading to frequency oscillations or periodic rhythm. Veratramine changed the chronotropic effect of K+ from weakly neg. to moderately pos. When half the Na+ or Cl- in the bathing medium was replaced by an impermeant ion, in the absence of veratramine the average heart rate was slightly decreased, whereas, in the presence of veratramine and periodic rhythm the average rate was increased, although the increase was not statistically significant in the case of low Na+. These observations indicate that Ca2+-induced Ca2+ release, Na+-Ca2+ exchange, and probably electrogenic Na+-K+ exchange play no important role in generation of periodic rhythm. The increased K+ dependence suggests an altered pacemaker mechanism.

IT 1166-01-4, Dichlorobenzamil
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(pharmacol. tests of the mechanism of the periodic rhythm caused by veratramine in the sinoatrial node of the guinea pig)

RN 1166-01-4 CAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



REFERENCE COUNT: 62 THERE ARE 62 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 38 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1997:137452 CAPLUS

DOCUMENT NUMBER: 126:246553

TITLE: Inhibition by 5-N-(4-chlorobenzyl)-2',4'-dimethylbenzamil of Na+/Ca2+ exchange and L-type Ca2+ channels in isolated cardiomyocytes

AUTHOR(S): Sharikabad, Mohammad Nouri; Cragoe, Edward. J., Jr.; Broers, Odd

CORPORATE SOURCE: Division of Clinical Pharmacology and Toxicology, Clinical Chemistry Department, Ullevaal University Hospital, Oslo, N-0407, Norway

SOURCE: Pharmacology & Toxicology (Copenhagen) (1997), 80(2), 57-61
CODEN: PHTOEH; ISSN: 0901-9928

PUBLISHER: Munksgaard

DOCUMENT TYPE: Journal

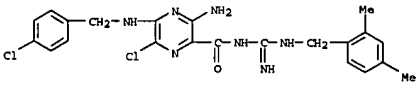
LANGUAGE: English

AB The inhibitory effect of the amiloride derivative 5-N-(4-chlorobenzyl)-2',4'-dimethylbenzamil (CBDMB) on calcium (Ca2+) uptake via sarcolemmal sodium-calcium (Na+/Ca2+) exchange and L-type Ca2+ channels was investigated in isolated adult rat ventricular cardiomyocytes under depolarizing conditions in cells preincubated with 1 mM ouabain or 137 mM lithium (Li+), resp. Fifteen or 120 min. preincubation with CBDMB inhibited Ca2+ uptake via Na+/Ca2+ exchange in Na+-loaded depolarized cells completely at 100 μM with an IC50 of 21 μM. After 120 min. preincubation, CBDMB inhibited Ca2+ uptake via L-type Ca2+ channels by 75.1% and IC50 of 4 μM, whereas no significant inhibition was observed after 15 min. preincubation. (+)-Isradipine (10 μM) inhibited high potassium (K+) induced Ca2+ uptake via L-type Ca2+ channels by 35% after 15 min. and by 70% after 120 min. preincubation. Inhibition by CBDMB of specific (+)-[3H]isradipine binding to L-type Ca2+ channels showed similar concentration dependency as inhibition of Ca2+ uptake via L-type Ca2+ channels. In conclusion, CBDMB inhibits sarcolemmal Na+/Ca2+ exchange in rat ventricular cardiomyocytes rapidly. However, after longer preincubation periods, L-type Ca2+ channels are inhibited as well and with higher potency than Na+/Ca2+ exchange.

IT 118573-60-7
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition by (4-chlorobenzyl)dimethylbenzamil of Na+/Ca2+ exchange and L-type Ca2+ channels in isolated cardiomyocytes)

RN 118573-60-7 CAPLUS

CN Pyrazinecarboxamide, 3-amino-6-chloro-5-[[[4-chlorophenyl)methyl]amino]-N-[[[(2,4-dimethylphenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



L6 ANSWER 39 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1996:285887 CAPLUS

DOCUMENT NUMBER: 125:872

TITLE: L-type Ca2+ channel and Na+/Ca2+ exchange inhibitors reduce Ca2+ accumulation in reperfused skeletal muscle

AUTHOR(S): Welsh, Donald G.; Lindinger, Michael I.

CORPORATE SOURCE: Department Human Biology and Nutritional Sciences, University Guelph, Guelph, ON, N1G 2W1, Can.

SOURCE: Journal of Applied Physiology (1996), 80(4), 1263-1269
CODEN: JAPHEV; ISSN: 8750-7587

PUBLISHER: American Physiological Society

DOCUMENT TYPE: Journal

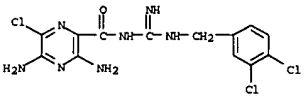
LANGUAGE: English

AB It is known that extracellular Ca2+ accumulates within skeletal muscle after prolonged periods of ischemia and reperfusion. In this study, we determined whether the L-type Ca2+ channel and the Na+/Ca2+ exchanger mediated Ca2+ influx and whether Ca2+ accumulation limited the metabolic and contractile recovery of reperfused skeletal muscle. Contracting rat hindlimbs (1-Hz twitch) exposed to 40 min of no-flow ischemia were reperfused with diltiazem (500 μM) or 3,4-dichlorobenzamil (300 μM) to block the Na+/Ca2+ exchanger and/or the L-type Ca2+ channel. High inhibitor concns. were used to counter the binding of diltiazem and 3,4-dichlorobenzamil to albumin and red blood cells. Muscle Ca2+ accumulation, contractile function, and energy metabolism were assessed by measuring intracellular Ca2+ concentration ([Ca2+]i), Ca2+ influx, twitch tension, and high-energy phosphagens [ATP, total adenine nucleotides (TAN) and phosphocreatine (PCr)]. Compared with control reperfusion, diltiazem and 3,4-dichlorobenzamil reduced Ca2+ influx and attenuated the rise in [Ca2+]i in the fast-oxidative glycolytic plantaris (Pl) and the fast-glycolytic white gastrocnemius (WG). The inhibitor-induced decrease in Ca2+ influx was 1.5- to 2-fold greater with 3,4-dichlorobenzamil than with diltiazem. Coinciding with the reduced Ca2+ accumulation, diltiazem and 3,4-dichlorobenzamil enhanced the resynthesis of ATP (Pl and WG), PCr (Pl and WG), and TAN (Pl) compared with control reperfusion. 3,4-Dichlorobenzamil also augmented twitch-tension recovery. We conclude that Ca2+ accumulation during reperfusion 1) arises from L-type Ca2+ channel and Na+/Ca2+ exchange activation; and 2) impairs the metabolic and contractile recovery of skeletal muscle.

IT 1166-01-4, Dichlorobenzamil
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(L-type Ca2+ channel and Na+/Ca2+ exchange inhibitors reduce Ca2+ accumulation in reperfused skeletal muscle)

RN 1166-01-4 CAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



L6 ANSWER 40 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1995:711442 CAPLUS

DOCUMENT NUMBER: 123:140200

TITLE: Non-selective effects of amiloride and its analogs on ion transport systems and their cytotoxicities in cardiac myocytes

AUTHOR(S): Murata, Yosuke; Harada, Kengo; Nakajima, Fumio; Maruo, Joji; Morita, Tominori

CORPORATE SOURCE: Dep. Biol., New Drug Res. Lab., Osaka, 534, Japan

SOURCE: Japanese Journal of Pharmacology (1995), 68(3), 279-85
CODEN: JJPAA2; ISSN: 0021-5198

PUBLISHER: Japanese Pharmacological Society

DOCUMENT TYPE: Journal

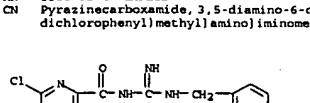
LANGUAGE: English

AB Effects of amiloride and its analogs (3',4'-dichlorobenzamil (DCB), 2',4'-dimethylbenzamil (DMB), 5-(N-ethyl-N-isopropyl)amiloride (EIPA) and 5-(N-methyl-N-isobutyl)amiloride (MIBA)) on cardiac ion transporters (Na+/Ca2+ exchanger, Na+/H+ exchanger, Na+ pump and Ca2+ pump) and their cytotoxicities were tested in cardiac myocytes. All the tested compds. showed concentration-dependent inhibitory effects on the ion transporters studied in canine cardiac sarcolemmal vesicles. The concns. (μM) of amiloride, DCB, DMB, EIPA and MIBA required to produce 50% inhibition were >100, 19, 10, 83 and 84, resp., for the Na+/Ca2+ exchanger; 130, 73, 63, 16 and 14 for the Na+/H+ exchanger; >100, 72, >300, >300 and >300 for the Na+ pump; and >1000, 37, 93, 90 and 70 for the Ca2+ pump, resp. Furthermore, these agents induced cell death in isolated rat cardiac myocytes and the 50% lethal concns. (μM) were >1000, 9.2, 30, 16 and 17, resp. These findings demonstrate that amiloride and its analogs have non-selective inhibitory effects on cardiac ion transporters and cytotoxicity in cardiomyocytes. When these drugs are employed as exptl. tools to investigate the involvement of ion transporters in cell functions, the results must be interpreted with caution.

IT 1166-01-4, 3',4'-Dichlorobenzamil 2093-13-2, 2',4'-Dimethylbenzamil
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(non-selective effects of amiloride and analogs on ion transport systems and cytotoxicities in cardiac myocytes)

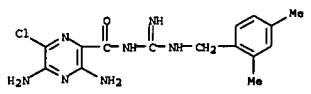
RN 1166-01-4 CAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)

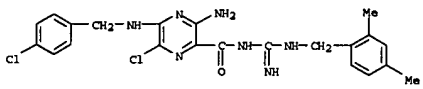


RN 2093-13-2 CAPLUS

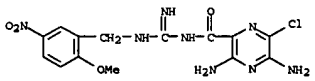
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2,4-dimethylphenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



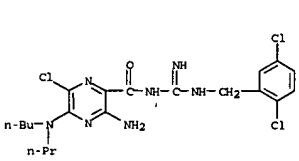
L6 ANSWER 41 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1994:645803 CAPLUS
DOCUMENT NUMBER: 121:245803
TITLE: The effect of inhibitors of Na/H exchange and Na/Ca exchange on airway smooth muscle contractility
AUTHOR(S): Knox, A. J.; Ajao, P.
CORPORATE SOURCE: Respiratory Med. Unit, City Hosp., Nottingham, NG5 1PB, UK
SOURCE: Pulmonary Pharmacology (1994), 7(2), 99-102
CODEN: PUPHEX; ISSN: 0952-0600
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We have previously shown that amiloride, an inhibitor of several cell membrane sodium exchangers and channels including Na/H exchange and Na/Ca exchange, inhibits receptor-operated contraction of bovine airway smooth muscle. However, the precise mechanism of action of amiloride is unknown. To evaluate the mechanism whereby amiloride reduces airway smooth muscle contractility, we compared the effects of amiloride with 5-N-Me iso-Bu amiloride and 5-N,N-hexamethylene amiloride, selective inhibitors of Na/H exchange, and 5-N(N-4-chlorobenzyl)-2,4-dimethylbenzamil, a selective inhibitor of Na/Ca exchange on histamine-induced contraction of bovine trachea. Unlike amiloride, none of the amiloride analogs, 5-N-Me iso-Bu amiloride (10 μmol/L), 5-N,N-hexamethylene amiloride (10 μmol/L) nor 5-N(N-4-chlorobenzyl)-2,4-dimethylbenzamil (20 μmol/L), inhibited histamine-induced contraction. Our results do not support the hypothesis that Na/H exchange or Na/Ca exchange are involved in histamine-induced contraction of airway smooth muscle.
IT 118573-60-7
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(the effect of inhibitors of Na/H exchange and Na/Ca exchange on airway smooth muscle contractility)
RN 118573-60-7 CAPLUS
CN Pyrazinecarboxamide, 3-amino-6-chloro-5-[[(4-chlorophenyl)methyl]amino]-N-[[[(2,4-dimethylphenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



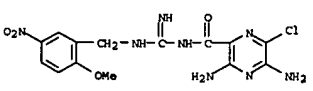
L6 ANSWER 42 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1994:260539 CAPLUS
DOCUMENT NUMBER: 120:260539
TITLE: Block by amiloride and its derivatives of mechanoelectrical transduction in outer hair cells of mouse cochlear cultures
AUTHOR(S): Rusch, A.; Kros, C. J.; Richardson, G. P.
CORPORATE SOURCE: Sch. Biol. Sci., Univ. Sussex, Falmer/Brighton, BN1 9QG, UK
SOURCE: Journal of Physiology (Cambridge, United Kingdom) (1994), 474(1), 75-86
CODEN: JPHYA7; ISSN: 0022-3751
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of amiloride and amiloride derivs. on mechanoelec. transducer currents in outer hair cells of the cultured neonatal mouse cochlea were examined under whole-cell voltage clamp. At -84 mV transducer currents were reversibly blocked by the extracellular application of the pyrazinecarboxamides amiloride, benzamil, dimethylamiloride, hexamethyleneiminoamiloride, phenamil and methoxynitroiodobenzamil with half-blocking concns. of 53, 5.5, 40, 4.3, 12 and 1.8 μM, resp. Hill coeffs. were determined for all but the last of these compds. and were 1.7, 1.6, 1.0, 2.2 and 1.6, resp., suggesting that two drug mols. co-operatively block the transducer channel. Both the structure-activity sequence for amiloride and its derivs. and the mechanism of the block of the transducer channel appear to be different from those reported for the high-affinity amiloride-sensitive epithelial Na+ channels but similar to those of stretch-activated channels in Xenopus oocytes. The block by all pyrazinecarboxamides was voltage dependent with pos. membrane potentials releasing the block. The form of the voltage dependence is consistent with a voltage-independent binding of the drug to a site that is accessible at hyperpolarized but not at depolarized potentials, suggesting that the transducer channel undergoes a voltage-dependent conformational change. The channel was not blocked by 1 mM amiloride from the intracellular side at either neg. or pos. membrane potentials. The kinetics of the block were studied using force steps or voltage jumps. The results suggest that the drug binding site is only accessible when the transducer channel is open (open-channel block) and that the channel cannot close when the drug mols. are bound. The time dependence and voltage dependence of the block together reveal that the transducer channel has at least two open conformational states, the transition between which is voltage dependent.
IT 122341-74-6 154707-31-0
RL: BIOL (Biological study)
(mechanoelec. transduction in outer hair cells of cochlear culture, blockade by, structure in relation to)
RN 122341-74-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[(2-methoxy-5-nitrophenyl)methyl]amino]methyl]-(9CI) (CA INDEX NAME)



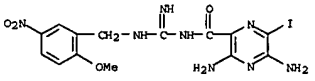
RN 154707-31-0 CAPLUS
CN Pyrazinecarboxamide, 3-amino-5-(butylpropylamino)-6-chloro-N-[[[(2,5-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



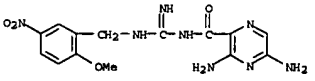
L6 ANSWER 43 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1994:156856 CAPLUS
DOCUMENT NUMBER: 120:156856
TITLE: Utilization of amiloride analogs for characterization and labeling of the plasma membrane Na+/H+ antiporter from Dunaliella salina
AUTHOR(S): Katz, Adriana; Kleyman, Thomas R.; Pick, Uri
CORPORATE SOURCE: Department of Biochemistry, Weizmann Institute of Science, Rehovot, 76100, Israel
SOURCE: Biochemistry (1994), 33(9), 2389-93
CODEN: BICHAW; ISSN: 0006-2960
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The interactions of amiloride analogs with the Na+/H+ antiporter from plasma membrane of the halotolerant alga Dunaliella salina were investigated. Analogs bearing hydrophobic substitutions at the guanidino moiety of amiloride, such as benzamil, are the most effective inhibitors of Na+ uptake in plasma membrane vesicles, whereas substituents of the 5-amino group are less effective inhibitors than amiloride. This order of specificity is opposite to that found for most Na+/H+ antiporters. The photoaffinity amiloride analog 2'-methoxy-5'-nitrobenzamil (NMBA), a competitive inhibitor with respect to Na+ with Ki = 10 μM, photolabels upon illumination 2 polypeptides of apparent mol. weight 30 and 50 kDa in purified plasma membrane vesicles. Similar labeling is obtained by immunodetection with antiamiloride antibodies and by incorporation of [125I]NMBA. The specificity of the labeling was ascertained by competition with benzamil. Plasma membrane prepns. from high-salt- or ammonia-adapted cells, which have higher Na+/H+ antiporter activity, also show increased incorporation of NMBA into the 30- and 50-kDa polypeptides. It is suggested that: (1) the structure of the Na+ binding site of the D. salina Na+/H+ antiporter differs from that of most Na+/H+ antiporters and (2) the 50- and/or 30-kDa polypeptides are subunits of the plasma membrane antiporter of this alga.
IT 122341-74-6 126671-77-0 153444-00-9
RL: BIOL (Biological study)
(sodium-hydrogen ion antiporter of Dunaliella salina inhibition by, structure in relation to)
RN 122341-74-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[(2-methoxy-5-nitrophenyl)methyl]amino]methyl]-(9CI) (CA INDEX NAME)



RN 126671-77-0 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[imino[[(2-methoxy-5-nitrophenyl)methyl]amino]methyl]-6-iodo-(9CI) (CA INDEX NAME)

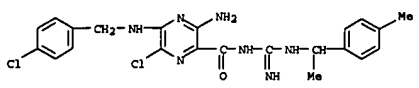


RN 153444-00-9 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[imino[[(2-methoxy-5-nitrophenyl)methyl]amino]methyl]-(9CI) (CA INDEX NAME)

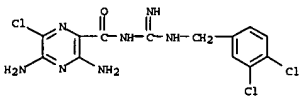


L6 ANSWER 44 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1994:74264 CAPLUS
DOCUMENT NUMBER: 120:74264
TITLE: Amiloride inhibition of angiogenesis in vitro
AUTHOR(S): Alliegro, Mark C.; Alliegro, Mary Anne; Cragoe, Edward J., Jr.; Glaser, Bert M.
CORPORATE SOURCE: Retina Cent., St. Joseph Hosp., Baltimore, MD, 21284, USA
SOURCE: Journal of Experimental Zoology (1993), 267(3), 245-52
CODEN: JEZOAO; ISSN: 0022-104X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Angiogenesis is important to such processes as normal embryonic development and tissue growth, and is also a central feature of diseases such as diabetic retinopathy and the growth of solid tumors. Understanding the basic events governing angiogenesis has therefore attracted great interest. The ion channel blocking agent, amiloride, has been shown previously to inhibit angiogenesis in an in vivo model. This suggested a vital role for Na+-coupled transport processes in angiogenesis. A large number of structural analogs of amiloride have been synthesized previously, and many of these are well characterized with respect to biol. activity. These analogs present an opportunity to dissect the process of angiogenesis and identify potentially important physiol. events. In the present report the authors describe the effects of amiloride on an in vitro model for angiogenesis employing vascularized tissue explants. Amiloride inhibits capillary morphogenesis completely and reversibly at concns. as low as 134 μM. It appears to act by blocking endothelial cell proliferation, but not migration. Inhibition is heightened by the introduction of hydrophobic groups on the terminal guanidino nitrogen atom, or on the 5-amino position. An analog substituted at both of these positions is 30-fold more potent than the parent compound. Of aniloride's known biol. activities, these results most closely correlate with the inhibition of Ca2+ transport processes, and thereby suggest an important role for Ca2+ transport in capillary morphogenesis.
IT 152306-15-5
RL: BIOL (Biological study)
(angiogenesis inhibition by, structure in relation to)
RN 152306-15-5 CAPLUS

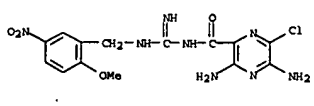
CN Pyrazinecarboxamide, 3-amino-6-chloro-5-[[(4-chlorophenyl)methyl]amino]-N-[imino[[1-(4-methylphenyl)ethyl]amino]methyl]-(9CI) (CA INDEX NAME)



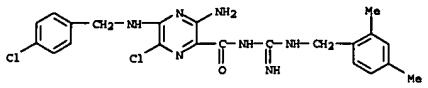
L6 ANSWER 45 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1994:3841 CAPLUS
DOCUMENT NUMBER: 120:3841
TITLE: Pyrazine compounds and the measurement of cytosolic calcium
AUTHOR(S): Kraut, Ricky P.; Greenberg, Arnold H.; Cragoe, Edward J., Jr.; Bose, Ratna
CORPORATE SOURCE: Manitoba Inst. Cell Biol., Univ. Manitoba, Winnipeg, MB, R3E 0W3, Can.
SOURCE: Analytical Biochemistry (1993), 214(2), 413-19
CODEN: ANBCA2; ISSN: 0003-2697
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Several of the pyrazine derivs. are widely used for inhibiting sodium flux via Na+/Ca2+ exchange or Na+/H+ exchangers or through the epithelial cation channels. These processes can profoundly affect cytosolic Ca2+. The authors found that the widely used fluorescent probes fura-2 and indo-1 could not be used to measure the effect of pyrazine analogs on the cytosolic free calcium ([Ca2+]i) of YAC-1 lymphoma cells treated with the pore-forming protein cytolysin/perforin. The authors show that the excitation spectra of pyrazine derivs. that specifically inhibit Na+/Ca2+ exchange [5-(N-4-chlorobenzyl)-2',4'-dimethylbenzamil],Na+/H+ exchange [5-(N-ethyl-N-isopropyl)-amiloride],and Na+ channels (phenamil) overlap with those of fura-2 and indo-1. In the presence of Ca2+, fluorescence readings for fura-2 plus drug are greater than those of fura-2 alone with the typically used 340- and 380-nm excitation light wavelengths; F380 readings were more affected than F340 readings. The effect was drug dose dependent. Hence, calcns. that use F340 readings in the presence of pyrazine derivs. will result in overests. of [Ca2+]i, while those that use the corresponding ratio readings, R340/380, will result in underests. of [Ca2+]i. The authors found that the luminescent intracellular Ca2+ indicator aequorin could be used successfully with pyrazine derivs. and that the ability of these compds. to enhance cytolysin/perforin-mediated increases in [Ca2+]i corresponded to their previously reported ability to inhibit Na+/Ca2+ exchange in pituitary cell plasma membrane vesicles. YAC-1 lymphoma cells are easy to culture and handle and may be a useful model for the studies of the Na+/Ca2+ exchanger in situ.
IT 118573-60-7
RL: ANST (Analytical study)
(calcium of cytosol response to, fluorescent calcium probes in relation to)
RN 118573-60-7 CAPLUS
CN Pyrazinecarboxamide, 3-amino-6-chloro-5-[[(4-chlorophenyl)methyl]amino]-N-[[[(2,4-dimethylphenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



L6 ANSWER 47 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1993:423369 CAPLUS
DOCUMENT NUMBER: 119:23369
TITLE: Structure-activity relations of amiloride derivatives, acting as antagonists of cation binding on Na+/K+-ATPase
AUTHOR(S): David, Peer; Mayan, Haim; Cragoe, Edward J., Jr.; Karlish, Steven J. D.
CORPORATE SOURCE: Dep. Biochem., Weizmann Inst. Sci., Rehovot, Israel
SOURCE: Biochimica et Biophysica Acta, Biomembranes (1993), 1146(1), 59-64
CODEN: BBBMBS; ISSN: 0005-2736
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In a search for an organic analog of K+ or Na+ ions that binds to the cation-binding sites of (Na+,K+)-ATPase with high affinity, the potency of the diuretic, amiloride, and its derivs. in blocking Rb+ occlusion was tested. Although amiloride itself had a low affinity (>200 μM), insertion of short alkyl chains in position 5 of the pyrazine ring of the mol. dramatically increased the affinity of the compound E.g., 5-(N-ethyl-N-isopropyl)amiloride(EIPA) competed with a Ki of .apprx.10 μM. In derivs. lacking a halogen in position 6 of the ring, a 6-fold decrease in affinity was found. Substitutions in the guanidinium moiety did not produce high-affinity inhibitors of Rb+ occlusion. Several derivs. at positions 5 and 6 of the pyrazine ring were found to be strictly competitive inhibitors with respect to Rb+. The highest affinity was observed at pH .apprx.8.0-8.2, and low temperature EIPA and 5-(N-methyl-N-isobutyl)amiloridestabilized the E1 form of FITC-labeled (Na+,K+)-ATPase, behaving as Na+ analogs. The present findings were similar to previous results, showing that alkyl- and arylguanidinium derivs. are competitive Na+-like antagonists in cation sites. Conclusions concerning the structural features of amiloride derivs. which are necessary to produce the highest binding affinity are being exploited in synthesis of competitive cation analogs. Derivs. with sufficiently high affinity (0.1-1 μM) will be converted to affinity and photoaffinity reagents.
IT 122341-74-6 126671-77-0
RL: BIOL (Biological study)
(ATPase of kidney monovalent cation binding inhibition by, structure in relation to)
RN 122341-74-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[(2-methoxy-5-nitrophenyl)methyl]amino]methyl]-(9CI) (CA INDEX NAME)

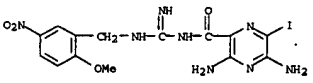


RN 126671-77-0 CAPLUS

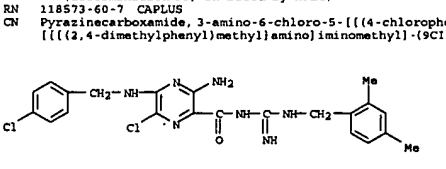


L6 ANSWER 46 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1993:531236 CAPLUS
DOCUMENT NUMBER: 119:131236
TITLE: Modulation of cardiac performance by amiloride and several selected derivatives of amiloride
AUTHOR(S): Pierce, Grant N.; Cole, William C.; Liu, Kanzhi; Massaeli, Hamid; Maddaford, Thane G.; Chen, Yi Jing; McPherson, Caroline D.; Jain, Shilpa; Sontag, David
CORPORATE SOURCE: Res. Cent., St. Boniface Gen. Hosp., Winnipeg, MB, Can.
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1993), 265(3), 1280-91
CODEN: JPETAB; ISSN: 0022-3565
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Amiloride and its derivs. (benzamil, dichlorobenzamil, 5-(N,N-dimethyl)-amiloride, 5-(N-ethyl-N-isopropyl)-amiloride, (N,N-hexamethylene)-amiloridesand 5-(N-methyl-N-isobutyl)-amiloride)are commonly used as selective blockers of Na+/Ca++ exchange or Na+/H+ exchange. Very little information is currently available regarding their effects on cardiac performance. It was observed that addition of amiloride or any of the selected derivs. to the coronary perfusate of the right ventricular wall produced a potent depressive effect on peak developed tension and the rates of tension generation and dissipation. The concns. at which this occurred are those that are commonly used in ischemia or hypoxia studies. Significantly, the depressive action of the drugs increased with the perfusion duration and never achieved a stable level. An initial, transient pos. inotropic effect was observed with some of the drugs. If the drug concentration and perfusion time was limited, the effects were reversible. All of the drugs except amiloride produced extra systoles. The drugs were capable of blocking Ca++ transients in isolated cardiomyocytes but had little effect on intracellular pH. The drugs lengthened the action potential duration and decreased the action potential amplitude and upstroke velocity. Their effects on cardiac performance may involve a complex inhibition of Ca++ influx and K+ efflux in addition to a stimulation of a nonselective cation current. It is concluded that amiloride and its analogs have striking effects on cardiac performance which may be unrelated to their capacity to inhibit Na+/Ca++ or Na+/H+ exchange. In summary, the use of these drugs is not normally recommended in cell or tissue perfusion expts. because of their nonselectivity. However, if the drug concentration and perfusion time is controlled carefully, interpretable data may be obtained in some cases.
IT 1166-01-4, Dichlorobenzamil
RL: BIOL (Biological study)
(heart contraction and elec. activity response to, calcium transport in relation to)
RN 1166-01-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)

CN Pyrazinecarboxamide, 3,5-diamino-N-[imino[[(2-methoxy-5-nitrophenyl)methyl]amino]methyl]-6-iodo-(9CI) (CA INDEX NAME)



L6 ANSWER 48 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1993:32441 CAPLUS
DOCUMENT NUMBER: 118:32441
TITLE: High-performance liquid chromatographic method for quantitating plasma levels of amiloride and its analogs
AUTHOR(S): Alliegro, Mary Anne; Dyer, Kimberly D.; Cragoe, Edward J., Jr.; Glaser, Bert M.; Alliegro, Mark C.
CORPORATE SOURCE: Retina Cent., St. Joseph Hosp., Baltimore, MD, 21284, USA
SOURCE: Journal of Chromatography (1992), 582(1-2), 217-23
CODEN: JOCRAM; ISSN: 0021-9673
DOCUMENT TYPE: Journal
LANGUAGE: English
AB An assay for amiloride was devised for efficient use with the wide variety of analogs available. Amiloride was extracted from 1-mL plasma sample by elution from a C8 preparative column with 6% acetonitrile-45% methanol-5.4% acetic acid, adjusted to pH 4.0 with trimethylamine. Samples were lyophilized, resuspended in 50% methanol, filtered through 0.22-μm Spin-X cartridges, applied to a reversed-phase C18 column, and eluted in a 0-50% acetonitrile gradient in 0.4% acetic acid, pH 4.5 (1.2 mL/min). Detection by UV absorbance at 360 nm was linear from 1 to 1000 ng. Versatility of the method was demonstrated with the analogs benzamil, 6-hydro-, 6-iodo-, 5-hexamethylene-, and 5-chlorobenzyl-2',4'-dimethylbenzylamiloride.
IT 118573-60-7
RL: ANT (Analyte); ANST (Analytical study)
(determination of, in blood by HPLC)
RN 118573-60-7 CAPLUS
CN Pyrazinecarboxamide, 3-amino-6-chloro-5-[[(4-chlorophenyl)methyl]amino]-N-[[[(2,4-dimethylphenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



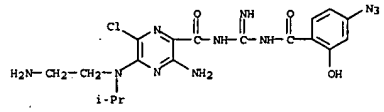
L6 ANSWER 49 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1992:605669 CAPLUS
DOCUMENT NUMBER: 117:205669
TITLE: Novel amiloride analog allosterically modulates the α2-adrenergic receptor but does not inhibit sodium/hydrogen ion exchange
AUTHOR(S): Wilson, Amy L.; Womble, Scott N.; Prakash, Chandra; Cragoe, E. J., Jr.; Blair, Ian A.; Limbird, Lee E.
CORPORATE SOURCE: Sch. Med., Vanderbilt Univ., Nashville, TN, 37332-6600, USA

SOURCE: Molecular Pharmacology (1992), 42(2), 175-9
CODEN: MOPMA3; ISSN: 0026-895X
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Two novel amiloride analogs have been synthesized during the course of efforts to develop a photoaffinity label for the amiloride allosteric domain on α2-adrenergic receptors. One of these, 5-[N-2'-aminoethyl-N'-isopropyl]amiloride-N-[4"-azidosalicylamide] (A-EIA-AS), markedly accelerates the rate of dissociation of [3H]yohimbine from affinity-purified α2-adrenergic receptors, an assay for allosteric modulation of receptor-adrenergic ligand interactions. In contrast, this agent does not appreciably inhibit Na+/H+ exchange, measured as 5-(N-ethyl-N-isopropyl)amiloride (EIA)-inhibitable 22Na+ uptake into cultured renal epithelial cells. A second analog, 5-[N"-2'-(4"-azidosalicylamidino)ethyl-N'-isopropyl]amilorid (ASA-EIA), does not foster an accelerated rate of dissociation of [3H]yohimbine binding from the α2 receptor but does block the ability of A-EIA-AS to do so, suggesting that ASA-EIA and A-EIA-AS interact at a common binding site. Interestingly, the ability of EIA to accelerate [3H]yohimbine dissociation is not blocked by ASA-EIA, a finding that may indicate that EIA and A-EIA-AS allosterically modulate α2 receptor-ligand interactions via distinct or nonoverlapping binding sites.

IT 144176-48-7
RL: BIOL (Biological study)
(adrenergic receptor modulation by, hydrogen ion-sodium exchange in relation to)

RN 144176-48-7 CAPLUS
CN Pyrazinecarboxamide, 3-amino-5-[(2-aminoethyl)(1-methylethyl)amino]-N-[[(4-azido-2-hydroxybenzoyl)amino]iminomethyl]-6-chloro-(9CI) (CA INDEX NAME)

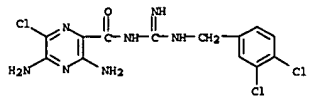


L6 ANSWER 50 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1992:584594 CAPLUS
DOCUMENT NUMBER: 117:184594
TITLE: Amiloride derivatives as blockers of sodium/calcium exchange: effects on mechanical and electrical function of guinea pig myocardium
AUTHOR(S): Wettwer, Erich; Himmel, Herbert; Ravens, Ursula
CORPORATE SOURCE: Dep. Pharmacol., Univ. Essen, Essen, D-4300/1, Germany
SOURCE: Pharmacology & Toxicology (Oxford, United Kingdom) (1992), 71(2), 95-102
CODEN: PHTOEH; ISSN: 0901-9928
DOCUMENT TYPE: Journal
LANGUAGE: English

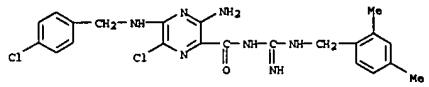
AB The amiloride derivs., 2',3'-benzobenzamil (BB), 3',4'-dichlorobenzamil (DCB), and 5-(N-4-chlorobenzyl)-2',4'-dimethylbenzamil(CBDB) are known as inhibitors of the Na+/Ca2+ exchange. This kind of drug action was recently suggested to be a new inotropic mechanism. In guinea-pig myocardium, the inotropic and the accompanying electrophysiol. effects of the three compds. were studied in order to assess their selectivity of action. In left atria and in papillary muscle, force of contraction increased with DCB and CBDB (atria only) at a high concentration (5•10-5-10-4 mol/L) and after long exposure time, whereas BB produced a neg. inotropic effect. In the isolated perfused Langendorff heart, the amiloride derivs. tested decreased spontaneous heart rate and force of contraction and prolonged the duration of contraction. In isolated cardiac myocytes, sodium current, calcium current and the delayed rectifier were reduced by concns. of BB, DCB and CBDB similar to the IC50 values reported for the inhibition of the Na+/Ca2+ exchange. These results demonstrate that the amiloride derivs. have multiple sites of action. It is concluded that more specific modulators of the Na+/Ca2+ exchange are required in order to define their contribution to the regulation of contractile activation of the heart.

IT 1166-01-4, 3',4'-Dichlorobenzamil 118573-60-7
RL: BIOL (Biological study)
(heart mech. and elec. functions response to, as sodium/calcium exchange blocker)

RN 1166-01-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



RN 118573-60-7 CAPLUS
CN Pyrazinecarboxamide, 3-amino-6-chloro-5-[[(4-chlorophenyl)methyl]amino]-N-[[[(2,4-dimethylphenyl]methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



L6 ANSWER 51 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1992:76385 CAPLUS
DOCUMENT NUMBER: 116:76385
TITLE: Use of amiloride and other pyrazine derivatives for preventing or treating ocular neovascularization
INVENTOR(S): Glaser, Bert M.; Varner, Hugh H.
PATENT ASSIGNEE(S): Baltimore Biotech, Inc., USA
SOURCE: Eur. Pat. Appl., 12 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

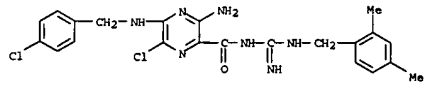
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 451130	A2	19911009	EP 1991-870055	19910404
EP 451130	A3	19920805		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
JP 07089859	A	19950404	JP 1991-73220	19910405
PRIORITY APPLN. INFO.:			US 1990-504584 A	19900405

AB Compns. and methods for treating ocular neovascularization use pyrazine derivs., especially amilorides. Amiloride-HCl.2H2O (I) inhibited neovascularization in a dose-dependent manner in rabbit corneas.

6-Iodoamiloride at 100 mM inhibited human urokinase-like plasminogen activator by 83.9%. Eye drop formulations containing I are presented.

IT 118573-60-7
RL: BIOL (Biological study)
(ocular neovascularization treatment with)

RN 118573-60-7 CAPLUS
CN Pyrazinecarboxamide, 3-amino-6-chloro-5-[[(4-chlorophenyl)methyl]amino]-N-[[[(2,4-dimethylphenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)

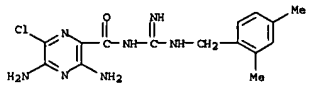


L6 ANSWER 52 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1991:623092 CAPLUS
DOCUMENT NUMBER: 115:223092
TITLE: Amiloride analogs induce responses in isolated rat cardiovascular tissues by inhibition of sodium/calcium exchange
AUTHOR(S): Brown, Lindsay; Cragoe, Edward J., Jr.; Abel, Keith C.; Manley, Simon W.; Bourke, John R.
CORPORATE SOURCE: Dep. Physiol. Pharmacol., Univ. Queensland, Brisbane, 4072, Australia
SOURCE: Naunyn-Schmiedeberg's Archives of Pharmacology (1991), 344(2), 220-4
CODEN: NSAPCC; ISSN: 0028-1298
DOCUMENT TYPE: Journal
LANGUAGE: English

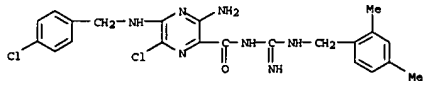
AB The role of inhibition of Na+/Ca2+ exchange in the pos. inotropic, neg. chronotropic and vasorelaxant responses to amiloride and some of its analogs was investigated in isolated cardiovascular tissues from female Wistar rats. The compds. tested were amiloride, 5-(N-ethyl-N-isopropyl)amiloride (EIPA, a potent inhibitor of Na+/H+ exchange), phenamil and 2',4'-dimethylbenzamil (DMB), both potent Na+ channel inhibitors with activity against Na+/Ca2+ exchange, and 5-(N-4-chlorobenzyl)-2',4'-dimethylbenzamil(CBDMB), a potent inhibitor of Na+/Ca2+ exchange with reduced activity against Na+ channels compared with its parent compound DMB. Phenamil, DMB and CBDMB increased the force of contraction of right ventricular papillary muscles with similar potencies (-log EC50 values: 4.77, 5.09, 4.97 resp.), while amiloride and EIPA gave small neg. inotropic responses. All compds. gave neg. chronotropic responses at similar concns. to those which exerted inotropic effects. Inhibition of KCl contraction of endothelium-free aortic rings was observed with all compds. tested. Phenamil, DMB and CBDMB but not amiloride or EIPA showed a shift to the left of the concentration-response curves in the presence of intact endothelium. These results provide further evidence for pos. inotropic and endothelium-dependent vasorelaxant effects of amiloride analogs mediated by inhibition of Na+/Ca2+ exchange.

IT 2093-13-2 118573-60-7
RL: PRP (Properties)
(inotropic and chronotropic and vasorelaxant effects of, in cardiovascular tissues, inhibition of sodium/calcium exchange in)

RN 2093-13-2 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2,4-dimethylphenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



RN 118573-60-7 CAPLUS
CN Pyrazinecarboxamide, 3-amino-6-chloro-5-[[(4-chlorophenyl)methyl]amino]-N-[[[(2,4-dimethylphenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)

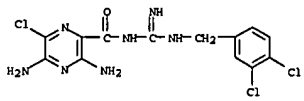


L6 ANSWER 53 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1991:550070 CAPLUS
DOCUMENT NUMBER: 115:150070
TITLE: Inhibition of the veratridine-induced increase in cytosolic calcium and respiration by Ca2+ antagonists in isolated cardiac myocytes
AUTHOR(S): Moreno-Sanchez, Rafael; Hanford, Richard G.
CORPORATE SOURCE: Dep. Bioquim., Inst. Nac. Cardiologia, Mexico City, 014080, Mex.
SOURCE: International Journal of Biochemistry (1991), 23(9), 889-96
CODEN: IJBOBV; ISSN: 0020-711X
DOCUMENT TYPE: Journal
LANGUAGE: English

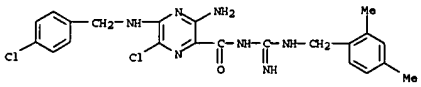
AB The effect of verapamil, nitrendipine, 3',4'-dichlorobenzamil (DCB) and Cd2+ on the increase in cytosolic free Ca2+ ([Ca2+]c) and the rate of O2-uptake induced by depolarization of isolated rat cardiac myocytes with veratridine was studied. The degree of inhibition by several drugs tested on the increase in [Ca2+]c and respiration was dependent on extracellular Ca2+, pH and Na+. Low verapamil and nitrendipine concns. (2.5 μM) were fully effective in Ca2+ channel blockade, as indicated from expts. with isoproterenol and in a low-Na+ medium. Complete inhibition of veratridine-induced increase in [Ca2+]c and O2-uptake was attained with higher Ca2+ blocker concns. (25-30 μM), implying that these processes depend to a major extent on some other Ca2+ transport system, probably Na+/Ca2+ exchange.

IT 1166-01-4, 3',4'-Dichlorobenzamil
RL: BIOL (Biological study)
(veratridine-induced increase in cytosolic calcium and respiration inhibition by, in cardiac myocytes)

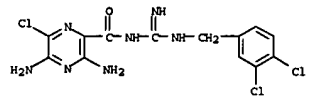
RN 1166-01-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



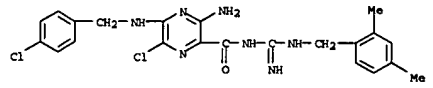
L6 ANSWER 54 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1991:442513 CAPLUS
DOCUMENT NUMBER: 115:42513
TITLE: Monovalent cation and amiloride analog modulation of adrenergic ligand binding to the unglycosylated α2B-adrenergic receptor subtype
AUTHOR(S): Wilson, Amy L.; Seibert, Karen; Brandon, Suzanne; Cragoe, E. J., Jr.; Limbird, Lee E.
CORPORATE SOURCE: Sch. Med., Vanderbilt Univ., Nashville, TN, 37232, USA
SOURCE: Molecular Pharmacology (1991), 39(4), 481-6
CODEN: MOPMA3; ISSN: 0026-895X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The unglycosylated α2B subtype of the α2-adrenergic receptor found in NG-108-15 cells possesses allosteric regulation of adrenergic ligand binding by monovalent cations and 5-amino-substituted amiloride analogs. These findings demonstrate that allosteric modulation of adrenergic ligand binding is not a property unique to the α2A subtype. The observation that amiloride analogs as well as monovalent cations can modulate adrenergic ligand binding to the nonglycosylated α2B subtype indicates that charge shielding due to carbohydrate moieties does not play a role in this allosteric modulation but, rather, these regulatory effects result from interactions of cations and amiloride analogs with the protein moiety of the receptor. Furthermore, the observation that both α2A and α2B receptor subtypes are modulated by amiloride analogs suggests that structural domains that are conserved between the 2 are likely to be involved in this allosteric modulation.
IT 118573-60-7
RL: BIOL (Biological study)
(α-adrenergic receptor subtype ligand binding modulation by, glycosylation in relation to)
RN 118573-60-7 CAPLUS
CN Pyrazinecarboxamide, 3-amino-6-chloro-5-[[(4-chlorophenyl)methyl]amino]-N-[[[(2,4-dimethylphenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



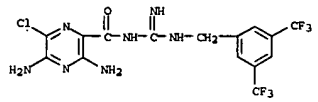
L6 ANSWER 55 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1991:441425 CAPLUS
DOCUMENT NUMBER: 115:41425
TITLE: Reversal of intrinsic multidrug resistance in Chinese hamster ovary cells by amiloride analogs
AUTHOR(S): Epand, R. F.; Epand, R. M.; Gupta, R. S.; Cragoe, E. J., Jr.
CORPORATE SOURCE: Health Sci. Cent., McMaster Univ., Hamilton, ON, L8N 3Z5, Can.
SOURCE: British Journal of Cancer (1991), 63(2), 247-51
CODEN: BJCAAI; ISSN: 0007-0920
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A number of amiloride analogs can sensitize wild type Chinese hamster ovary (CHO) cells to the cytotoxic action of vinblastine, daunomycin, puromycin or colchicine. Some of these analogs also have weak sensitizing effects on the multidrug resistant CHO cell line, CHRC5. The unusual feature of most of the active amiloride analogs is that they are more potent in reversing the intrinsic multidrug resistance (MDR) phenotype of CHO cells than their acquired MDR characteristic. Human HeLa cells that do not exhibit intrinsic MDR are not affected by these agents. Several of the amiloride analogs have a greater effect in increasing adriamycin uptake in wild type CHO cells than they do with CHRC5 cells. The differential effect of amiloride analogs on intrinsic vs. acquired MDR characteristics of Chinese hamster cells suggests some differences in the underlying resistance mechanisms.
IT 1166-01-4 118573-60-7 118593-88-7 134788-24-2
RL: BIOL (Biological study)
(multiple resistance to neoplasm inhibitors inhibition by)
RN 1166-01-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



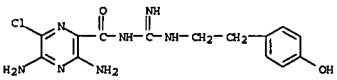
RN 118573-60-7 CAPLUS
CN Pyrazinecarboxamide, 3-amino-6-chloro-5-[[(4-chlorophenyl)methyl]amino]-N-[[[(2,4-dimethylphenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



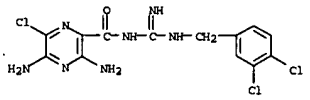
RN 118593-88-7 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[[3,5-bis(trifluoromethyl)phenyl]methyl]amino]iminomethyl]-6-chloro-(9CI) (CA INDEX NAME)



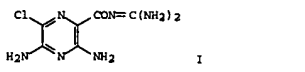
RN 134788-24-2 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[2-(4-hydroxyphenyl)ethyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



L6 ANSWER 56 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1991:422747 CAPLUS
DOCUMENT NUMBER: 115:22747
TITLE: Inhibition of sodium/calcium exchange in pancreatic islet cells by 3',4'-dichlorobenzamil
AUTHOR(S): Plasman, Pierre Olivier; Lebrun, Philippe; Cragoe, Edward J., Jr.; Herchuelz, Andre
CORPORATE SOURCE: Sch. Med., Brussels Univ., Brussels, B-1000, Belg.
SOURCE: Biochemical Pharmacology (1991), 41(11), 1759-68
CODEN: BCPCA6; ISSN: 0006-2952
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Na/Ca exchange may play a role in Ca2+ extrusion from the pancreatic B cell. The role played by the exchanger was examined by characterizing the effects of 3',4'-dichlorobenzamil on ionic fluxes and insulin release in normal rat pancreatic islet cells. 3',4'-Dichlorobenzamil potently inhibited 45Ca uptake mediated by reverse Na/Ca exchange (IC50:18 μM) in islet cells. The drug failed to decrease intracellular pH but reduced 86Rb outflow fromperfused islets. The effects of glucose and 3',4'-dichlorobenzamil on 86Rb outflow were not additive. The drug potently blocked 45Ca uptake through voltage-sensitive Ca2+ channels (IC50:7.5 μM). In the presence of extracellular Ca2+ and 3',4'-dichlorobenzamil, glucose lost part of its ability to reduce 45Ca outflow. The drug failed to affect the secondary rise in 45Ca outflow induced by the sugar. In the absence of extracellular Ca2+, 3',4'-dichlorobenzamil induced a delayed inhibition of 45Ca outflow, the effects of the sugar and the drug were not additive. This effect of 3',4'-dichlorobenzamil and its ability to impair the inhibitory effect of glucose were reproduced by the removal of extracellular Na+. 3',4'-Dichlorobenzamil did not effect insulin release in the absence of glucose, but it increased glucose-induced insulin release when used at a high concentration Although, 3',4'-dichlorobenzamil is a potent inhibitor of Na/Ca exchange in the pancreatic B cell, the drug is of poor specificity and blocks both K+ channels and voltage-sensitive Ca2+ channels in the same range of concns. The data also indicate that glucose inhibits 45Ca outflow from pancreatic islets to a great extent (at least 75%) by inhibiting Na/Ca exchange. The type of Na/Ca exchange that is inhibited by glucose remains to be elucidated.
IT 1166-01-4, 3',4'-Dichlorobenzamil
RL: BIOL (Biological study)
(calcium and sodium exchange by pancreatic islet inhibition by, glucose-induced insulin release in relation to)
RN 1166-01-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)

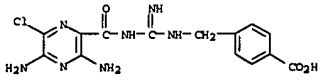


L6 ANSWER 57 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1991:199065 CAPLUS
DOCUMENT NUMBER: 114:199065
TITLE: Distinct epitopes on amiloride. II. Variably restricted epitopes defined by monoclonal anti-amiloride antibodies
AUTHOR(S): Kleyman, Thomas R.; Zebrowitz, Joseph R.
CORPORATE SOURCE: Dep. Med., Univ. Pennsylvania, Philadelphia, PA, 19104, USA
SOURCE: American Journal of Physiology (1991), 260(2, Pt. 1), C271-C276
CODEN: AJPHAP; ISSN: 0002-9513
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

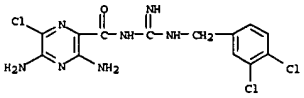


I

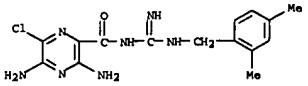
AB Specific regions of amiloride (I) appear to participate in binding to receptors on amiloride sensitive transport proteins. Previous studies characterizing epitopes on amiloride recognized by antiamiloride antibodies have demonstrated that antibodies recognize specific domains on amiloride and that these epitopes are determined, in part, by the site on amiloride used to couple to carrier protein. The 3,5-diaminopyrazinyl and guanidinocarbonyl moieties were identified as distinct epitopes. Since Na+-selective transport proteins are sensitive to changes of the halide on the amiloride mol., addnl. monoclonal anti-amiloride antibodies were raised to determine whether the C-6 halo group of amiloride could be identified as an important site for drug-antibody binding. The epitopes recognized by a series of three monoclonal antibodies raised against amiloride coupled to rabbit serum albumin through its C-5 NH2-group were defined. Two antibodies recognize extensive regions on the amiloride mol., including both the acylguanidino and pyrazinyl groups. In addition, both antibodies are sensitive to changes in the C-6 halo group on amiloride. A third antibody was relatively insensitive to changes in the halide in the C-6 position of the pyrazine ring of amiloride and recognized a more restricted epitope on amiloride.
IT 133481-24-0
RL: BIOL (Biological study)
(binding to transporting proteins, distinct epitopes role in, structure in relation to)
RN 133481-24-0 CAPLUS
CN Benzoic acid, 4-[[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]methyl]- (9CI) (CA INDEX NAME)



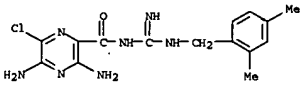
L6 ANSWER 58 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1991:178103 CAPLUS
DOCUMENT NUMBER: 114:178103
TITLE: Inhibition of sodium-calcium and sodium-proton exchangers by amiloride congeners in arterial muscle cells
AUTHOR(S): Smith, Jeffrey Bingham; Lyu, Rong Ming; Smith, Lucinda
CORPORATE SOURCE: Sch. Med., Univ. Alabama, Birmingham, AL, 35294, USA
SOURCE: Biochemical Pharmacology (1991), 41(4), 601-9
CODEN: BCPCA6; ISSN: 0006-2952
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The inhibitory potencies of several amiloride congeners towards Na+-Ca2+ and Na+-H+ exchange were compared in rat aortic myocytes. N-(2,4-Dimethylbenzyl)amiloride(DMB) was 10 times more potent towards Na+-Ca2+ than Na+-H+ exchange. Amiloride and ethylisopropylamiloridewere about 5,000 and 10,000 times more potent towards Na+-H+ than Na+-Ca2+ exchange resp. N-(3,4-Dichlorobenzyl)amiloridewas almost equipotent towards both exchangers. About 40 nM ethylisopropylamiloride inhibited Na+-H+ exchange by 50%. Ethylisopropylamiloride (10 μM) had no effect on basal or angiotensin-evoked 45Ca2+ efflux or net Ca2+ efflux. In contrast to ethylisopropylamiloride, 25-50 μM DMB, which strong inhibits Na+-Ca2+ exchange, markedly decreased both 45Ca2+ efflux and net Ca2+ efflux produced by angiotensin. Replacing extracellular Na+ with N-methyl-D-glucamine inhibited angiotensin-evoked 45Ca2+ efflux similarly to DMB. Neither DMB nor Na+ placement had any effect on basal or angiotensin evoked production of [3H]inositol phosphates. These findings suggest that Na+-H+ exchange has no major influence on short-term Ca2+ regulation by vasoconstrictors and provide evidence that Na+-Ca2+ exchange is a major pathway or rapid Ca2+ efflux in stimulated arterial muscle cells.
IT 1166-01-4 2093-13-2
RL: BIOL (Biological study)
(sodium-calcium and sodium-proton exchangers inhibition by, in arterial muscle cells)
RN 1166-01-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



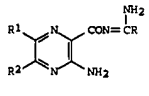
RN 2093-13-2 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2,4-dimethylphenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



L6 ANSWER 59 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1991:17865 CAPLUS
DOCUMENT NUMBER: 114:17865
TITLE: Sodium-calcium exchange activity in central nerve endings. II. Relationship between pharmacological blockade by amiloride analogs and dopamine release from tuberoinfundibular hypothalamic neurons
AUTHOR(S): Taglialatela, Maurizio; Canzoniero, Lorella M. T.; Cragoe, Edward J., Jr.; Di Renzo, Gianfranco; Annunziato, Lucio
CORPORATE SOURCE: 2nd Sch. Med., Univ. Naples, Naples, 80131, Italy
SOURCE: Molecular Pharmacology (1990), 38(3), 393-400
CODEN: MOPMA3; ISSN: 0026-895X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The aim of the present study was to investigate the possible role played by the Na+-Ca2+ exchange system in the modulation of [3H]dopamine ([3H]DA) release from tuberoinfundibular hypothalamic (TIDA) neurons. 2',4'-Dimethylbenzamil (DMB) dose-dependently (10-100 μM) inhibited Na+-dependent 45Ca2+ efflux from brain synaptosomes. This compound (30-300 μM), as well as α-phenylbenzamil amiloride (30-100 μM), another inhibitor of the Na+-Ca2+ antiporter, was also able to stimulate basal release of [3H]DA from superfused TIDA neurons. This stimulation was completely prevented by the removal of extracellulra Ca2+ ions, in the presence of 1 mM ethylene glycol bis(β-aminoethyl ether)-N,N,N',N'-tetraceticacid. In addition, DMB-induced [3H]DA release was unaffected by the dopamine transport inhibitor nomifensine (10 μM). On the other hand, 5-[N-methyl-N-guanidinocarbonylmethyl]amiloride(MGCMA) (100-300 μM), which lacks inhibitory properties on the Na+-Ca2+ exchanger but behaves as an inhibitor of the Na+-H+ antiporter, failed to modify basal [3H] DA release from TIDA neurons. When the Na+-Ca2+ antiporter operates as a Ca2+ influx pathway, as occurs upon the removal of extracellular Na+ ions, Na+-dependent 45Ca2+ uptake in brain synaptosomes was dose-dependently (10-300 μM) inhibited by DMB, whereas DMB itself was unable to prevent 55 mM K+-induced 45Ca2+ uptake, which mainly reflects the activation of voltage-operated Ca2+ channels. In keeping with these results, ouabain (500 μM)-induced [3H]DA release, which depends on the activation of the Na+-Ca2+ exchanger due to inhibition of the Na+-K+-ATPase pump, was prevented by superfusion of TIDA neurons with DMB (50 μM). By contrast, MGCMA (100 μM) failed to modify either Na+-dependent 45Ca2+ influx or ouabain-induced [3H]DA release. Evidently, the pharmacol. inhibition of the Na+-Ca2+ antiporter by amiloride analogs affect DA release from central neurons. Opposite effects are observed, depending on the direction of operation of the exchanger. In fact, when the Na+-Ca2+ exchanger operates as a Ca2+ efflux pathway, its pharmacol. blockade can produce a stimulation of DA release. In contrast, when this antiporter operates as a Ca2+ influx pathway, as occurs as a consequence of the inhibition of the Na+-K+-ATPase pump by ouabain, its pharmacol. blockade can prevent ouabain-induced DA release from TIDA neurons.
IT 2093-13-2
RL: BIOL (Biological study)
(dopamine release by tuberoinfundibular hypothalamic neuron response to, sodium-calcium exchange in relation to)
RN 2093-13-2 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2,4-dimethylphenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)

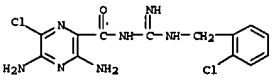


L6 ANSWER 60 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1991:178 CAPLUS
DOCUMENT NUMBER: 114:178
TITLE: Effects of amiloride analogs on human erythroleukemic K562 cell growth and on induction of hemoglobin synthesis by adriamycin
AUTHOR(S): Steinfeld, Richard C.; Severski, Matthew C.; Cragoe, Edward J., Jr.; Knauf, Philip A.
CORPORATE SOURCE: Sch. Med. Dent., Univ. Rochester, Rochester, NY, 14642, USA
SOURCE: Experimental Hematology (New York, NY, United States) (1990), 18(7), 818-23
CODEN: EXHMA6; ISSN: 0301-472X
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

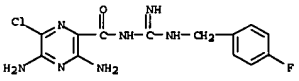


I

AB Treatment with adriamycin for 8-14 h irreversibly induced K562 human erythroleukemic cells to synthesize Hb. With 16-h exposure, this effect is maximal at concns. between 180 and 400 nM, yielding 70%-90% benzidine-pos. (B+) cells and 24 pg/cell Hb 4 days after the beginning of adriamycin treatment. This induction is accompanied by changes in ouabain-sensitive 86Rb influx opposite to those seen with murine erythroleukemic (MEL) cells. Amiloride and several amiloride analogs I (R1 = halo; R2 = H, amino, or substituted amino; R = amino or substituted amino) strongly inhibit adriamycin induction of Hb synthesis as well as cell growth in the absence of adriamycin. The inhibition of induction is enhanced with the analogs bearing a benzyl or substituted benzyl group on the 5-amino or on a terminal guanidino nitrogen atom. The effect on growth was somewhat greater with the analog bearing a 2-chlorobenzyl moiety on a terminal guanidino nitrogen atom and with the one bearing a 2-fluorobenzyl group on the 5-amino nitrogen atom. The structural features required for growth inhibition resemble those seen with MEL cells, but the features required for inhibition of induction of Hb synthesis are completely different. These data suggest that different specific binding sites are involved in these two effects of amiloride and its analogs.
IT 1163-44-6, 2'-Chlorobenzamil 1634-16-8, 4'-Fluorobenzamil
RL: BIOL (Biological study)
(erythroleukemic cells of humans growth and Hb formation induction by adriamycin response to, structure in relation to)
RN 1163-44-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2-chlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)

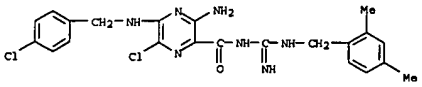


RN 1634-16-8 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(4-fluorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)

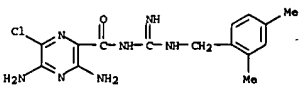


L6 ANSWER 61 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1990:628530 CAPLUS
DOCUMENT NUMBER: 113:228530
TITLE: Stimulation of calcium uptake into epididymal bull spermatozoa by analogs of amiloride
AUTHOR(S): Breitbart, Haim; Cragoe, Edward J.; Lardy, Henry A.
CORPORATE SOURCE: Dep. Life Sci., Bar-Ilan Univ., Ramat-Gan, 52900, Israel
SOURCE: European Journal of Biochemistry (1990), 192(2), 529-35
CODEN: EJBCAI; ISSN: 0014-2956
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Certain amiloride analogs 3',4'-dichlorobenzamil (I), 2',4'-dimethylbenzamil, and α',2'-benzobenzamil hydrochloride (ATBB) stimulate Ca2+ accumulation and motility by epididymal bovine spermatozoa. This stimulation can be seen at a range of 0.1-0.4 mM, but at higher concentration there is inhibition of Ca2+ uptake by these amiloride analogs. The amiloride derivative 5-(4-chlorobenzyl)-2',4'-dimethylbenzamil(CBDMB), which bears a 4-chlorobenzyl substituent on the 5-amino N atom, did not stimulate Ca2+ uptake. I inhibits the Na+/Ca2+-exchange activity in isolated plasma membrane vesicles, and the stimulatory effect of I on Ca2+ uptake into epididymal sperm could be seen in Na+-free medium. Thus, the stimulation of Ca2+ accumulation in the cells caused by I is not a result of inhibiting the Na+-dependent Ca2+ clearance. There is no stimulation of Ca2+ uptake into ejaculated cells by adding I, which is not due to the presence of Ca2+-transport inhibitor (caltrin) in these cells (Rufo, G. A.; et al., 1984). The stimulatory effect of I on Ca2+ uptake is inhibited by the voltage-dependent Ca2+-channel blockers nifedipin and diltiazem. Apparently, the stimulation of Ca2+ uptake by the amiloride analog is due to the activation of a voltage-dependent Ca2+ channel of the plasma membrane.
IT 118573-60-7
RL: BIOL (Biological study)
(calcium uptake by epididymal sperm in relation to)

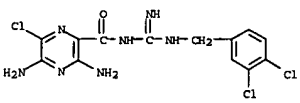
RN 118573-60-7 CAPLUS
CN Pyrazinecarboxamide, 3-amino-6-chloro-5-[[[(4-chlorophenyl)methyl]amino]-N-[[[(2,4-dimethylphenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



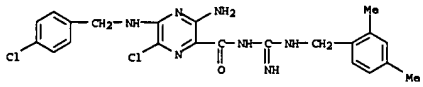
IT 2093-13-2
RL: BIOL (Biological study)
(calcium uptake by epididymal sperm stimulation by)
RN 2093-13-2 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2,4-dimethylphenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



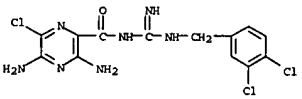
IT 1166-01-4, 3',4'-Dichlorobenzamil
RL: BIOL (Biological study)
(calcium uptake stimulation and sodium-calcium exchange inhibition by, in epididymal sperm)
RN 1166-01-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



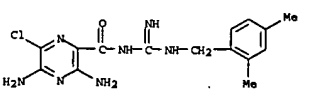
L6 ANSWER 62 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1990:624910 CAPLUS
DOCUMENT NUMBER: 113:224910
TITLE: The hydrophobic tryptic core of the porcine α2-adrenergic receptor retains allosteric modulation of binding by sodium, hydrogen ion, and 5-amino-substituted amiloride analogs
AUTHOR(S): Wilson, Amy L.; Guyer, Cheryl A.; Cragoe, Edward J., Jr.; Limbird, Lee E.
CORPORATE SOURCE: Sch. Med., Vanderbilt Univ., Nashville, TN, 37232-6600, USA
SOURCE: Journal of Biological Chemistry (1990), 265(28), 17318-22
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Extensive trypsinization of the purified α2-adrenergic receptor and repurifn. by wheat germ agglutinin-agarose chromatog. yields an adrenergic ligand-binding hydrophobic core of the receptor. Allosteric modulation of adrenergic ligand binding by Na+, H+, and 5-amino substituted analogs of amiloride is quant. retained in this core, as assessed by the ability of these agents to accelerate the rate of [3H]yohimbine dissociation from the adrenergic ligand-binding site. These findings refine the understanding of where within the α2-adrenergic receptor structure these allosteric agents bind and, for the effects of Na+ and H+, allow certain predictions to be made as to which carboxylic acid side chains are probable candidates for participation in a monovalent cation-binding pocket within the hydrophobic tryptic core of the receptor.
IT 118573-60-7
RL: BIOL (Biological study)
(adrenergic ligand binding by α2-adrenergic receptor tryptic core inhibition by)
RN 118573-60-7 CAPLUS
CN Pyrazinecarboxamide, 3-amino-6-chloro-5-[[[(4-chlorophenyl)methyl]amino]-N-[[[(2,4-dimethylphenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



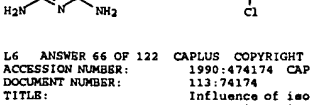
L6 ANSWER 63 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1990:584863 CAPLUS
DOCUMENT NUMBER: 113:184863
TITLE: Interaction of amiloride and its analogs with adenosine A1 receptors in calf brain
AUTHOR(S): Garritsen, Anja; IJzerman, Ad P.; Beukers, Margot W.; Cragoe, Edward J., Jr.; Soudijn, Willem
CORPORATE SOURCE: Div. Med. Chem., Cent. Bio-Pharm. Sci., Leiden, 2300 RA, Neth.
SOURCE: Biochemical Pharmacology (1990), 40(4), 827-34
CODEN: BCPCA6; ISSN: 0006-2952
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Amiloride, a K sparing diuretic, is known to interact with a number of ion transport systems, receptors and enzymes. The interaction between this drug and the adenosine A1 receptor as present in calf brain membranes is reported. Adenosine A1 receptors are characterized by a subnanomolar affinity for the antagonist [3H]8-cyclopentyl-1,3-dipropylxanthine ([3H]DPCPX) and the agonist [3H]N6-R-1-phenyl-2-propyladenosine ([3H])PIA). Amiloride displaces both agonist and antagonist binding with a Ki value in the low micromolar range. This inhibition is counteracted by NaCl and protons, in contrast to the binding of [3H]PIA and [3H]DPCPX. Thus, amiloride interacts with the adenosine A1 receptor at a site distinct from the ligand binding site. In order to elucidate the role of one of the ion transport systems known to be inhibited by amiloride, 8 amiloride analogs with different sensitivities for these systems were tested. The potency and order of potency of these compds. towards adenosine A1 receptors excludes the involvement of the epithelial Na+ channel, Na+/H+ exchanger, or Na+/Ca2+ exchanger.
IT 1166-01-4, 3',4'-Dichlorobenzamil
RL: BIOL (Biological study)
(purinergic A1 receptor binding of, in brain, ion transport in relation to)
RN 1166-01-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



L6 ANSWER 64 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1990:545079 CAPLUS
DOCUMENT NUMBER: 113:145079
TITLE: Amiloride analogs induce the phosphorylation of elongation factor-2 in vascular endothelial cells
AUTHOR(S): Demolle, D.; Lecomte, M.; Boutherin-Falson, O.; Cragoe, E. J., Jr.; Nairn, A. C.; Boeynaems, J. M.
CORPORATE SOURCE: Sch. Med., Univ. Libre Bruxelles, Brussels, Belg.
SOURCE: Molecular Pharmacology (1990), 37(6), 827-32
CODEN: MOPMA3; ISSN: 0026-895X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB 5-(N-Ethyl-N-isopropyl)amiloride(EIPA), a potent inhibitor of Na+/H+ antiport, reduced [35]methionine incorporation in proteins and induced the phosphorylation of a 95,000 dalton protein in bovine aortic endothelial cells. This protein is phosphorylated in response to ATP, bradykinin, and A23187 and is identified as elongation factor-2. The action of EIPA was independent of changes in cytosolic pH, because it was neither mimicked by sodium acetate nor inhibited by ammonium chloride, and it was reproduced by 2',4'-dimethylbenzamil, an analog of amiloride that is inactive on the Na+/H+ antiport. EIPA enhanced the Ca2+-dependent phosphorylation of a similar 95,000 dalton protein in a cell-free rabbit reticulocyte lysate where an inhibitory effect of amiloride on protein synthesis is known. Because phosphorylation decreases the activity of elongation factor-2, the observations might explain why amiloride analogs inhibit protein synthesis.
IT 2093-13-2
RL: BIOL (Biological study)
(elongation factor 2 phosphorylation response to, in endothelium)
RN 2093-13-2 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2,4-dimethylphenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



L6 ANSWER 65 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1990:530557 CAPLUS
DOCUMENT NUMBER: 113:130557
TITLE: A role for sodium/calcium exchange in the generation of superoxide radicals by human neutrophils
AUTHOR(S): Simchowitz, Louis; Foy, Margaret A.; Cragoe, Edward J., Jr.
CORPORATE SOURCE: Dep. Med., Veterans Adm. Med. Cent., St. Louis, MO, 63106, USA
SOURCE: Journal of Biological Chemistry (1990), 265(23), 13449-56
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A Na+/Ca2+ exchange mechanism has been recently described in human neutrophils that constitutes the principal pathway for Ca2+ influx into resting cells. The potential role of this system in regulating the respiratory burst in response to activation by the chemotactic tripeptide N-formyl-methionyl-leucyl-phenylalaninewas explored. In the presence of 1 mM Ca2+, a variety of di- and trivalent cations suppressed the generation of O2- radicals in a series of decreasing efficacy: La3+ .apprx. Zn2+ > Sr2+ .apprx. Cd2+ > Ba2+ > Co2+ > Ni2+ .apprx. Mg2+. This sequence is similar to their rank order of activity in inhibiting 45Ca2+ influx via Na+/Ca2+ counter-transport. Benzamil, phenamil, and 2',4'-dichlorobenzamil, analogs of amiloride which selectively block Na+/Ca2+ exchange in neutrophils, likewise suppressed the release of O2- with apparent Ki values of .apprx.30 μM. The effect of the cations was competitive with Ca2+, while the interaction between the benzamil derivs. and Ca2+ appeared to be noncompetitive in nature. Both the divalent cations and benzamil also inhibited the rise in cytoplasmic Ca2+ as monitored by fura-2 fluorescence: these agents reduced peak cytosolic Ca2+ levels after N-formyl-methionyl-leucyl-phenylalaninestimulation to values seen in the absence of extracellular Ca2+. These results are compatible with the hypothesis that the influx of Ca2+ via Na2+/Ca2+ exchange contributes to the transient elevation in extracellular free Ca2+. The polyvalent cations block the entry of critical Ca2+ ions by competing with Ca2+ for binding to the translocation site on the exchange carrier, while benzamil acts by lowering the maximal transport rate. These studies emphasize that Na+/Ca2+ exchange through its effects on cytoplasmic Ca2+ plays a major regulatory role in activation of the respiratory burst in chemotactic factor-stimulated neutrophils.
IT 90689-42-2, 2',4'-Dichlorobenzamil
RL: BIOL (Biological study)
(calcium/sodium exchange in human neutrophils response to, superoxide formation in relation to)
RN 90689-42-2 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)

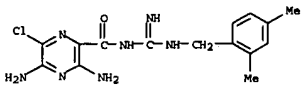


L6 ANSWER 66 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1990:474174 CAPLUS
DOCUMENT NUMBER: 113:74174
TITLE: Influence of isolation media on synaptosomal properties: intracellular pH, pCa, and calcium uptake
AUTHOR(S): Bandeira-Duarte, C.; Carvalho, C. A. M.; Cragoe, E. J., Jr.; Carvalho, A. P.
CORPORATE SOURCE: Inst. Histol. Embriol., Univ. Coimbra, Coimbra, 3049, Port.
SOURCE: Neurochemical Research (1990), 15(3), 313-20
CODEN: NERED2; ISSN: 0364-3190
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Prepns. of synaptosomes isolated in sucrose or in Na+-rich media were compared with resp. to internal pH (pHi), internal Ca2+ concentration ([Ca2+]i),

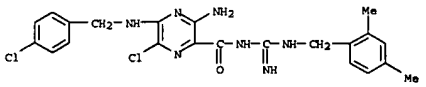
membrane potential, and 45Ca2+ uptake due to K+ depolarization and Na+/Ca2+ exchange. Synaptosomes isolated in sucrose media have a pHi of 6.77 ±0.04 and a [Ca2+]i of about 260 nM, whereas synaptosomes isolated in Na+-rich ionic media have a pHi of 6.96 ± 0.07 and a [Ca2+]i of 463 nM, but both types of prepns. have similar membrane potentials of about -50 mV when placed in choline media. The sucrose preparation takes up Ca2+ only by voltage sensitive calcium channels (VSCC'S) when K+-depolarized, while the Na+-rich synaptosomes take up 45Ca2+ both by VSCC'S and by Na+/Ca2+ exchange. The amiloride derivative 2',4'-dimethylbenzamil (DMB), at 30 μM, inhibits both mechanisms of Ca2+ influx, but 5-(N-4-chlorobenzyl)-2',4'dimethylbenzamil (CBS-DMB), at 30 μM, inhibits the Ca2+ uptake by VSCC'S, but not by Na+/Ca2+ exchange. Thus, DMB and CBZ-DMB permit distinguishing between Ca2+ flux through channels and through Na+/Ca2+ exchange. The different properties of the two types of synaptosomes studied account for some of the discrepancies in results reported in the literature for studies of Ca2+ fluxes and neurotransmitter release by different types of prepns. of synaptosomes.

IT 2093-13-2 118573-60-7
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(synaptosomes response to)

RN 2093-13-2 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2,4-dimethylphenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



RN 118573-60-7 CAPLUS
CN Pyrazinecarboxamide, 3-amino-6-chloro-5-[[(4-chlorophenyl)methyl]amino]-N-[[[(2,4-dimethylphenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)

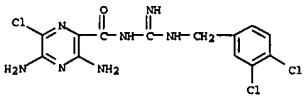


L6 ANSWER 67 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1990:470716 CAPLUS
DOCUMENT NUMBER: 113:70716
TITLE: Influence of amiloride derivatives on alpha-1 adrenergic receptor-induced contractions of the rabbit aorta
AUTHOR(S): Lesburg, Charles; Li, Shauna; Cragoe, Edward J., Jr.; Deth, Richard C.
CORPORATE SOURCE: Coll. Pharm. Allied Health Profess., Northeastern Univ., Boston, MA, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1990), 253(2), 530-6
CODEN: JPETAB; ISSN: 0022-3565
DOCUMENT TYPE: Journal
LANGUAGE: English

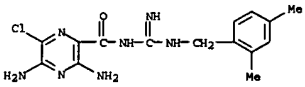
AB Derivs. of amiloride that exhibit greater specificity for inhibition of either Na+/H+ or Na+/Ca++ exchange were evaluated for their ability to influence phenylephrine (PE)-induced contractions of the rabbit aorta. Most, but not all, derivs. with alkyl substituents at the 5-amino position (which exhibit greater potency for Na+/H+ exchange inhibition) caused a dose-dependent contraction at concns. above 10 μM. At higher concns. and longer incubation times this contraction reached 70 to 80% of the maximal PE response. Contractions induced by 5-amino-substituted amiloride derivs. were dependent upon extracellular Ca++ and were inhibited by either extracellular acidification or intracellular alkalinization. This suggests that they resulted from an influence of intracellular acidification on Ca++ transport. Contractile responses to PE (1 μM) were reduced by most but not all 5-amino-substituted derivs. in conjunction with tension development. Dimethylamiloride, however, failed to cause a contraction at doses up to 100 μM but was the most potent inhibitor of PE-induced contractions among the 5-amino derivs. Dose-response curves for PE were shifted both to the right and downward by increasing concns. of amiloride, which indicates both competitive and noncompetitive types of inhibition. Guanidino-substituted derivs. such as benzobenzamil were the most potent antagonists, producing noncompetitive inhibition in excess of 90% at a concentration of 10 μM. The differing patterns of inhibition as well as the presence or absence of intrinsic contractile activity indicate that amiloride derivs. have the potential for multiple pathways of action that modify arterial contractility.

IT 1166-01-4, Dichlorobenzamil 2093-13-2
128505-64-6
RL: BIOL (Biological study)
(α1-adrenoceptor-induced artery contraction inhibition by, ion transport in)

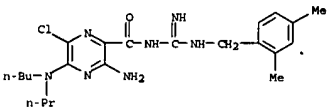
RN 1166-01-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



RN 2093-13-2 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2,4-dimethylphenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



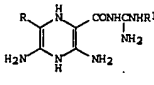
RN 128505-64-6 CAPLUS
CN Pyrazinecarboxamide, 3-amino-5-(butylpropylamino)-6-chloro-N-[[[(2,4-dimethylphenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



L6 ANSWER 68 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1990:229739 CAPLUS
DOCUMENT NUMBER: 112:229739
TITLE: Treating diseases characterized by hyperexcitability of neurons with pyrazinoylguanidines
INVENTOR(S): Morad, Martin; Tang, Cha Min
PATENT ASSIGNEE(S): University of Pennsylvania, USA
SOURCE: U.S., 11 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 4894376	A	19900116	US 1988-160835	19880226

PRIORITY APPLN. INFO.: US 1988-160835 19880226
OTHER SOURCE(S): MARPAT 112:229739
GI

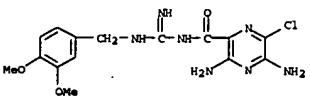


I

AB The pyrazinoylguanidines I [R = halo; R1 = H, alkyl, (un)substituted Bz] are T-type Ca channel blockers, useful for the treatment of title diseases, such as epilepsy and painful neuropathy. Amiloride (250 μM) selectively suppressed the T-type calcium channel in mouse adrenal gland (NIE-115) neuroblastoma cells, in vitro.

IT 127367-37-7
RL: BIOL (Biological study)
(calcium channel blocker, for treatment of neuron-hyperexcitability diseases)

RN 127367-37-7 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dimethoxyphenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)

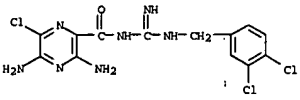


L6 ANSWER 69 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1990:213213 CAPLUS
DOCUMENT NUMBER: 112:213213
TITLE: Amiloride analogs inhibit L-type calcium channels and display calcium entry blocker activity
AUTHOR(S): Garcia, Maria L.; King, V. Frank; Shevell, Judith L.; Slaughter, Robert S.; Suarez-Kurtz, Guilherme; Winquist, Raymond J.; Kaczorowski, Gregory J.
CORPORATE SOURCE: Dep. Membr. Biochem. Biophys., Merck Inst. Ther. Res., Rahway, NJ, 07065, USA
SOURCE: Journal of Biological Chemistry (1990), 265(7), 3763-71
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English

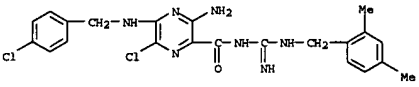
AB Three structural classes of commonly used amiloride analogs, mols. derivatized at the terminal guanidino-N, the 5-position pyrazinoyl-N, or di-substituted at both of these positions, inhibit binding of the L-type Ca2+ channel modulators, diltiazem, gallopamil, and nitrendipine to porcine cardiac sarcolemmal membrane vesicles. The rank order of inhibitory potencies among the various derivs. tested is well defined, with amiloride being the least potent. Saturation binding studies indicate that inhibition of ligand binding results primarily from effect on Kd. Ligand dissociation measurements suggest that amiloride derivs. do not associate directly at any of the known sites in the Ca2+ entry blocker receptor complex. In addition, these compds. do not compete at the Ca2+ coordination site within the channel. However, studies with inorg. and substituted diphenylbutylpiperidine Ca2+ entry blockers reveal that amiloride analogs interact at a site on the channel where metal ions bind and occlude the pore. Photolysis expts. performed with amiloride photoaffinity reagents confirm that a specific interaction occurs between such probes and the channel protein. Upon photolysis, these agents produce concentration- and time-dependent irreversible inactivation of Ca2+ entry blocker binding activities, which can be protected against by either verapamil or diltiazem. 45Ca2+ flux and voltage-clamp expts. performed with GH3 anterior pituitary cells demonstrate that amiloride-like compds. inhibit L-type Ca2+ channels directly. Moreover, these compds. block contraction of isolated vascular tissue in pharmacol. assays. Electrophysiol. expts. indicate that they also inhibit T-type Ca2+ channels in GH3 cells. Taken together, these results demonstrate unequivocally that amiloride analogs display significant Ca2+ entry blocker activity in both ligand binding and functional assays. This property, therefore, can seriously complicate the interpretation and many in vitro and in vivo studies where amiloride analogs are used to elicit inhibition of other transport systems (e.g., Na-Ca and Na-H exchange).

IT 1166-01-4, L 594881 118573-60-5, L 651525
122341-74-6, L 648865 126671-77-C, L 663126
126671-78-1, L 663128 126820-86-6, L 652165
RL: ANST (Analytical study)
(calcium channel-mediated transport by sarcolemma of heart inhibition by)

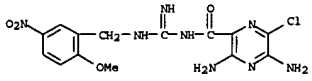
RN 1166-01-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



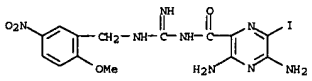
RN 118573-60-7 CAPLUS
CN Pyrazinecarboxamide, 3-amino-6-chloro-5-[[(4-chlorophenyl)methyl]amino]-N-[[[(2,4-dimethylphenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



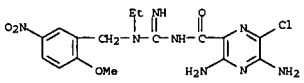
RN 122341-74-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[(2-methoxy-5-nitrophenyl)methyl]amino]methyl]-(9CI) (CA INDEX NAME)



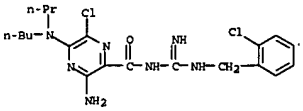
RN 126671-77-0 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[imino[[(2-methoxy-5-nitrophenyl)methyl]amino]methyl]-6-iodo-(9CI) (CA INDEX NAME)



RN 126671-78-1 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[ethyl[(2-methoxy-5-nitrophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)

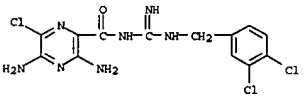


RN 126820-86-8 CAPLUS
CN Pyrazinecarboxamide, 3-amino-5-(butylpropylamino)-6-chloro-N-[[[(2,?-dichlorophenyl)methyl]amino]iminomethyl]-(9CI)* (CA INDEX NAME)



D1-Cl

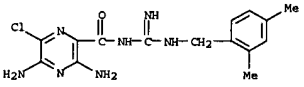
L6 ANSWER 70 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1990:210841 CAPLUS
DOCUMENT NUMBER: 112:210841
TITLE: Inhibition of taste responses to sodium salts by epithelial sodium channel blockers in gerbil
AUTHOR(S): Schiffman, Susan S.; Suggs, Mark S.; Cragoe, Edward J., Jr.; Erickson, Robert P.
CORPORATE SOURCE: Dep. Psychiatry, Duke Univ., Durham, NC, 27706, USA
SOURCE: Physiology & Behavior (1990), 47(3), 455-9
CODEN: PHBHA4; ISSN: 0031-9384
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The Na+ transport inhibitor amiloride blocks taste responses to NaCl by 60-70%. The purpose of the present study was to determine if greater inhibition could be achieved with 3 potent amiloride analogs that are specific for the epithelial Na+ channel: phenamil, 2',4'-dimethylbenzamil, and 3',4'-dichlorobenzamil. Application of phenamil (100 μM) to the anterior tongue blocked integrated responses to NaCl from the chorda tympani nerve by 98.04%, but had no significant effect on sucrose or NH4Cl. This finding suggests that the epithelial Na+ channel alone transduces the taste of NaCl in gerbil. The residual 30-40% of the response that is not blocked by amiloride can simply be explained by the fact that amiloride is less potent than phenamil. On average, 100 μM phenamil blocked responses to Na+ salts with a variety of anions by 94.2%; 100 μM 2',4'-dimethylbenzamil, by 89.83%; and 100 μM 3',4'-dichlorobenzamil, by 72.56%. Small residual responses to salts of glutamate and phosphate were not eliminated by the amiloride analogs; this suggests that other transduction mechanisms may account for a small portion of taste responses for these salts in the gerbil.
IT 1166-01-4, 3',4'-Dichlorobenzamil 127134-23-0
RL: BIOL (Biological study)
(sodium channel response to, salty taste perception in relation to)
RN 1166-01-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



RN 127134-23-0 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2,4-dimethylphenyl)methyl]amino]iminomethyl]-,compd. with 2-propanol (1:1) (9CI) (CA INDEX NAME)

CM 1

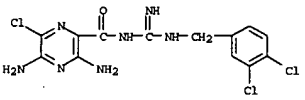
CRN 2093-13-2
CMF C15 H18 Cl N7 O



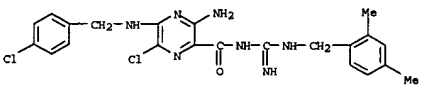
CM 2

CRN 67-63-0
CMF C3 H8 O

L6 ANSWER 71 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1990:210840 CAPLUS
DOCUMENT NUMBER: 112:210840
TITLE: The effect of amiloride analogs on taste responses in gerbil
AUTHOR(S): Schiffman, Susan S.; Frey, Amy E.; Suggs, Mark S.; Cragoe, Edward J., Jr.; Erickson, Robert P.
CORPORATE SOURCE: Dep. Psychol., Duke Univ., Durham, NC, 27706, USA
SOURCE: Physiology & Behavior (1990), 47(3), 435-41
CODEN: PHBHA4; ISSN: 0031-9384
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Amiloride analogs that were designed to inhibit 3 types of Na+ transport systems (the epithelial Na+ channel, the Na+/H+ antiporter, and the Na+/Ca++ exchanger) were applied to the tongue of the gerbil to determine their effects on electrophysiol. responses to NaCl, CaCl2, sucrose, and glutamic acid. The pattern of responses from the chorda tympani nerve indicates that the taste of NaCl is almost totally accounted for by the epithelial Na+ channel. Phenamil, an amiloride analog which specifically blocks the epithelial Na+ channel at low concns., suppressed the taste responses to 0.03 M NaCl by 97%. The pattern of responses also indicates that the Na+/H+ antiporter and the Na+/Ca2+ exchanger do not mediate salt taste in the gerbil. None of the amiloride analogs blocked taste responses to CaCl2, sucrose, or glutamic acid. It is concluded that the salty taste of NaCl in the gerbil is almost totally mediated by the epithelial Na+ channel, and the kinetics of this channel are identical to amiloride-sensitive Na+ channels in other systems.
IT 1166-01-4, 3',4'-Dichlorobenzamil 118573-60-7
127134-23-0
RL: BIOL (Biological study)
(sodium channel in mediation of salty taste response to)
RN 1166-01-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



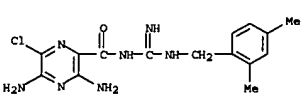
RN 118573-60-7 CAPLUS
CN Pyrazinecarboxamide, 3-amino-6-chloro-5-[[(4-chlorophenyl)methyl]amino]-N-[[[(2,4-dimethylphenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



RN 127134-23-0 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2,4-dimethylphenyl)methyl]amino]iminomethyl]-,compd. with 2-propanol (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 2093-13-2
CMF C15 H18 Cl N7 O



CM 2

CRN 67-63-0
CMF C3 H8 O

L6 ANSWER 72 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1990:409 CAPLUS
DOCUMENT NUMBER: 112:409
TITLE: Comparison of the effect of amiloride and its analog dichlorobenzamil on cardiac chronotropic responses to ouabain in myocardial cell aggregates in culture
AUTHOR(S): Rabkin, Simon W.
CORPORATE SOURCE: Cardiovasc. Res. Lab., Univ. Hosp. (Shaughnessy), Vancouver, BC, V6H 3N1, Can.
SOURCE: Pharmacology (1989), 39(4), 230-9

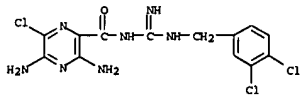
CODEN: PHMGBN; ISSN: 0031-7012
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The purpose of this study was to compare the effects of amiloride, an inhibitor of Na+-H+ exchange, and its analog 3',4'-dichlorobenzamil, a more specific inhibitor of Na+-Ca2+ exchange, on the response of cardiac myocytes to ouabain. Cardiac myocyte aggregates were prepared from myocytes obtained from 7-day-old chick embryo hearts. Ouabain at 10-6M produced a marked reduction in contractile frequency. Amiloride at 10-7-10-5M produced a definite and concentration-dependent reduction in this effect of ouabain. In contrast, dichlorobenzamil, 10-7-10-6, accentuated this effect of ouabain. Thus, amiloride and its analog dichlorobenzamil have different effects on the cardiac responses to ouabain, presumably because of the differences in the specificity of their inhibition of Na+-H+ and Na+-Ca2+ exchange. Thus to the extent that the effects of amiloride and dichlorobenzamil are mediated through, respectivewly Na+-H+ and Na+-Ca2+ exchange, these data suggest that ouabain-induced reduction in contractile frequency is mediated through Na+-H+ exchange, while Na+-Ca2+ exchange acts to minimize this action of ouabain. Amiloride may be useful to oppose the neg. chronotropic effect of ouabain, while dichlorobenzamil accentuates this effect of ouabain.

IT 1166-01-4, 3',4'-Dichlorobenzamil
RL: BIOL (Biological study)
(heart myocyte chronotropic response to ouabain response to)

RN 1166-01-4 CAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



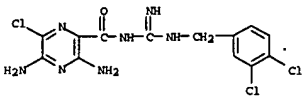
L6 ANSWER 73 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1989:609045 CAPLUS
DOCUMENT NUMBER: 111:209045
TITLE: Inhibition of sodium-calcium exchange by general anesthetics
AUTHOR(S): Haworth, Robert A.; Goknur, Atilla B.; Berkoff, Herbert A.
CORPORATE SOURCE: Clin. Sci. Cent., Univ. Wisconsin, Madison, WI, 53792, USA
SOURCE: Circulation Research (1989), 65(4), 1021-8
CODEN: CIRUAL; ISSN: 0009-7330
DOCUMENT TYPE: Journal
LANGUAGE: English

AB General anesthetics, typically octanol, were found to inhibit the influx of calcium in isolated sodium-loaded adult rat heart cells, using 45Ca, quin 2, or indo 1. Inhibition by octanol, like inhibited by sodium, was competitive with calcium. Octanol and sodium together inhibited calcium influx synergistically. At physiol. levels of extracellular calcium and sodium, the EC50 was 177 μM for octanol and 48 μM for decanol. These values are 3-fold to 4-fold larger than those reported to cause 50% loss of righting reflex in tadpoles, a measure of their anesthetic effectiveness. General anesthetics inhibit Na-Ca exchange at the sarcolemma. Octanol inhibits like sodium, and the synergism stems from the cooperativity of sodium inhibition at the binding and regulatory sites of the exchanger. Insofar as Na-Ca exchange may regulate inotropy, the inhibition of Na-Ca exchange by general anesthetics could contribute to their neg. inotropic effect.

IT 1166-01-4, Dichlorobenzamil
RL: BIOL (Biological study)
(calcium-sodium exchange response to, in heart)

RN 1166-01-4 CAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



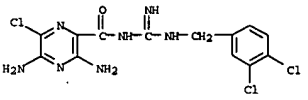
L6 ANSWER 74 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1989:608931 CAPLUS
DOCUMENT NUMBER: 111:208931
TITLE: The effect of amiloride and its analog dichlorobenzamil on the cardiac chronotropic responses of myocardial cell aggregates in culture to alterations of extracellular potassium or calcium
AUTHOR(S): Rabkin, Simon W.
CORPORATE SOURCE: Cardiovasc. Res. Lab., Univ. British Columbia, Vancouver, BC, V6T 1W5, Can.
SOURCE: General Pharmacology (1989), 20(5), 595-600
CODEN: GEPHDP; ISSN: 0306-3623
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Cardiac ventricular myocyte aggregates from 7-day-old chick embryos exhibited a decrease in beating rate with increasing [K+] from 1 to 10 mM, and stopped beating at 10 mM. Amiloride, at 10-7 and 10-6M, produced an accentuation of the effects of increasing [K+] that was concentration-dependent, and it produced an earlier cessation of spontaneous beating. The amiloride analog 3',4'-dichlorobenzamil (DCB), that preferentially inhibits Na+/Ca2+ exchange, produced an accentuation of the effects of [K+] that was greater than that produced by amiloride. When [Ca2+] was increased from 2.2 to 5.0 mM, cardiac beating rate increased, became irregular and then stopped at [Ca2+] of 5 mM. DCB, but not amiloride, accentuated the changes with increasing [Ca2+]. Thus inhibition of Na+-Ca2+ exchange accentuates the effect of increased [Ca2+] on the heart.

IT 1166-01-4, 3',4'-Dichlorobenzamil
RL: BIOL (Biological study)
(heart chronotropic response to potassium or calcium response to)

RN 1166-01-4 CAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



L6 ANSWER 75 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN

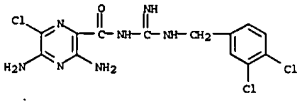
ACCESSION NUMBER: 1989:567014 CAPLUS
DOCUMENT NUMBER: 111:167014
TITLE: Blockade of endothelin-induced contractions by dichlorobenzamil: mechanism of action
AUTHOR(S): Criscione, Leoluca; Thomann, Helene; Rodriguez, Candido; Egleme, Cecile; Chiesi, Michele
CORPORATE SOURCE: Pharm. Div., Ciba-Geigy Ltd., Basel, 4002, Switz.
SOURCE: Biochemical and Biophysical Research Communications (1989), 163(1), 247-54
CODEN: BBRCA9; ISSN: 0006-291X
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Contraction of intact rat aortic rings induced by endothelin were totally inhibited by the amiloride analog dichlorobenzamil (DCB) at concns. known to block Na-Ca exchange. Amiloride (100 μM) was ineffective. Ca-channel blockers and a K-channel opener elicited only partial inhibition. These results could indicate that the Na-Ca exchanger plays an important role in endothelin-induced contractions. Endothelin, however, had no effect on the kinetics of the exchanger, and, in addition, contractions also occurred in Na-depleted vessels. The endothelin-induced contractions produced by Ca release from intracellular pools were also completely inhibited by DCB. The latter compound was found to block contraction induced by Ca itself in the presence of Ca ionophore or detergent. DCB acts directly on Ca-induced activation of myofilaments in smooth muscle.

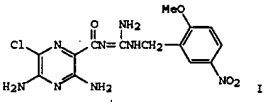
IT 1166-01-4, Dichlorobenzamil
RL: BIOL (Biological study)
(endothelin-induced contractions in aortic rings inhibition by, calcium channels in relation to)

RN 1166-01-4 CAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



L6 ANSWER 76 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1989:527221 CAPLUS
DOCUMENT NUMBER: 111:127221
TITLE: The cellular pool of sodium channels in the amphibian cell line A6 is not altered by mineralocorticoids. Analysis using a new photoactive amiloride analog in combination with anti-amiloride antibodies
AUTHOR(S): Kleyman, Thomas R.; Cragoe, Edward J., Jr.; Kraehenbuhl, Jean Pierre
CORPORATE SOURCE: Dep. Med., Columbia Univ., New York, NY, 10032, USA
SOURCE: Journal of Biological Chemistry (1989), 264(20), 11995-2000
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



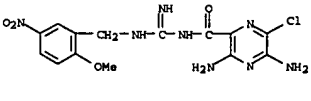
I

AB An amiloride-sensitive Na+ channel is found in the apical plasma membrane of high resistance, Na+ transporting epithelia. A method for the identification of this channel based on the use of a new high affinity photoreactive amiloride analog, 2'-methoxy-5'-nitrobenzamil (I; NMBA), and anti-amiloride antibodies to identify photolabeled polypeptides is described. NMBA specifically labels the putative Na+ channel in bovine kidney microsomes. A 130-kDa polypeptide is detected on immunoblots with anti-amiloride antibodies. NMBA is a potent inhibitor of Na+ transport in the established amphibian kidney epithelial cell line A6, and specifically labels a 130-kDa polypeptide. Both NMBA photolabeling and [3H]benzamil binding were used to examine the cellular pool of putative channels following hormonal regulation of Na+ transport. This pool is not significantly altered by the mineralocorticoid agonist aldosterone or antagonist spironolactone, despite a 3.8-fold difference in transepithelial Na+ transport.

IT 122341-74-6
RL: BIOL (Biological study)
(sodium channels labeling by, in kidney cortex and tight epithelium)

RN 122341-74-6 CAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[(2-methoxy-5-nitrophenyl)methyl]amino]methyl]-(9CI) (CA INDEX NAME)



L6 ANSWER 77 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1989:490035 CAPLUS
DOCUMENT NUMBER: 111:90035
TITLE: Chemical modification of cell proliferation and fluid secretion in renal cysts
AUTHOR(S): Grantham, Jared J.; Uchic, Marie; Cragoe, E. J., Jr.; Kornhaus, James; Grantham, J. Aaron; Donoso, Vicki; Mangoo-Karim, Roberto; Evan, Andrew; McAteer, James
CORPORATE SOURCE: Sch. Med., Univ. Kansas, Kansas City, KS, USA
SOURCE: Kidney International (1989), 35(6), 1379-89
CODEN: KDYIA5; ISSN: 0085-2538
DOCUMENT TYPE: Journal
LANGUAGE: English

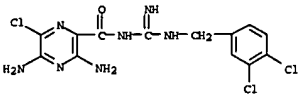
AB The authors used an in vitro model, MDCK cyst, to determine the extent to which pharmacol. compds. known to inhibit plasma membrane solute transport mechanisms could alter the enlargement of renal epithelial cysts. Amiloride and seven amiloride analogs that inhibited to different degrees conductive Na+ transport, Na+-dependent H+ transport and Na+-dependent Ca++ transport reversibly decreased the rate of cyst enlargement. The effectiveness of these agents to retard cyst enlargement correlated with their relative potencies to inhibit Na+-dependent Ca++ transport. Morphol. examination indicated that amiloride and amiloride analogs decreased

cell proliferation and fluid secretion to the same degree. Ouabain and vanadate (Na + K,ATPase inhibitors), and L-645,695 (Na+-dependent Cl-/HCO3- inhibitor) potently slowed cyst expansion. In contrast to amiloride and amiloride analogs, these agents caused an unusual degree of cellular stratification within the cyst walls, a finding consistent with the notion that fluid secretion was inhibited to a greater extent then cellular proliferation. Chemical inhibitors of primary and secondary active solute transport can diminish or halt the enlargement of epithelial cysts in vitro by decreasing the rate of cellular proliferation and/or net fluid secretion.

IT 1166-01-4, 3',4'-Dichlorobenzamil 118573-60-7
RL: BIOL (Biological study)
(kidney cyst enlargement inhibition by)

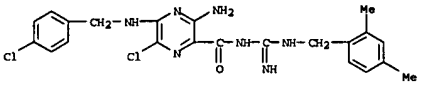
RN 1166-01-4 CAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



RN 118573-60-7 CAPLUS

CN Pyrazinecarboxamide, 3-amino-6-chloro-5-[[(4-chlorophenyl)methyl]amino]-N-[[[(2,4-dimethylphenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



L6 ANSWER 78 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1989:207935 CAPLUS

DOCUMENT NUMBER: 110:207935

TITLE: Kinetic properties of the sodium/hydrogen ion antiport of heart mitochondria

AUTHOR(S): Brierley, Gerald P.; Davis, Michael H.; Cragoe, Edward J., Jr.; Jung, Dennis W.

CORPORATE SOURCE: Med. Cent., Ohio State Univ., Columbus, OH, 43210, USA

SOURCE: Biochemistry (1989), 28(10), 4347-54
CODEN: BICHAW; ISSN: 0006-2960

DOCUMENT TYPE: Journal

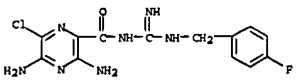
LANGUAGE: English

AB The fluorescence of 2',7'-bis(carboxyethyl)-5(6)-carboxyfluorescein (BCECF) was used to follow the Na+/H+ antiport activity of isolated heart mitochondria as a Na+-dependent extrusion of matrix H+. The antiport activity measured in this way shows a hyperbolic dependence on external Na+ or Li+ concentration when the external pH (pHo) is ≥7.2. The apparent Km for Na+ decreases with increasing pHo to a limit of 4.6 mM. The Ki for external H+ as a competitive inhibitor of Na+/H+ antiport ave. 3.0 nM (pHo 8.6). The Vmax at 24° is 160 ng H+/min/mg protein and does not vary with pHo. Li+ reacts with the antiporter with higher affinity, but much lower Vmax, and is a competitive inhibitor of Na+/H+ antiport. The rate of Na+/H+ antiport is optimal when the internal pH (pHi) is near 7.2. When pHo is maintained constant, Na+-dependent extrusion of matrix H+ shows a hyperbolic dependence on [H+]i with an apparent Km corresponding to a pHi of 6.8. The Na+/H+ antiport is inhibited by benzamil and by 5-N-substituted amiloride analogs with I50 values in the range from 50 to 100 μM. The pH profile for this inhibition seems consistent with the availability of a matrix-binding site for the amiloride analogs. The mitochondrial Na+/H+ antiport resembles the antiport found in the plasma membrane of mammalian cells in that Na+, Li+, and external H+ appear to compete for a common external binding site and both exchanges are inhibited by amiloride analogs. However, there are significant differences in the sensitivity of the 2 antiports to these inhibitors, and the mitochondrial exchanger appears to operate in a more alkaline region than the plasmalemmal component. The increased affinity of the antiport for Na+ with increasing pH is in line with the putative role of this exchanger as a device for extruding Na+ from the alkaline matrix of respiring mitochondria.

IT 1634-16-8
RL: BIOL (Biological study)
(antiport of protons and sodium by heart mitochondria inhibition by)

RN 1634-16-8 CAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(4-fluorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



L6 ANSWER 79 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1989:187890 CAPLUS

DOCUMENT NUMBER: 110:187890

TITLE: High levels of sodium-calcium exchange in vascular smooth muscle sarcolemmal membrane vesicles

AUTHOR(S): Slaughter, Robert S.; Shevell, Judith L.; Felix, John P.; Garcia, Maria L.; Kaczorowski, Gregory J.

CORPORATE SOURCE: Dep. Membrane Biochem. Biophys., Merck Inst. Therapeut. Res., Rahway, NJ, 07065, USA

SOURCE: Biochemistry (1989), 28(9), 3995-4002
CODEN: BICHAW; ISSN: 0006-2960

DOCUMENT TYPE: Journal

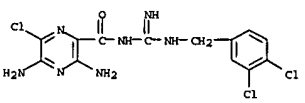
LANGUAGE: English

AB Membrane vesicles which exhibit high levels of Nai-dependent Ca2+ uptake have been prepared from either porcine or bovine aortic smooth muscle. These membranes are identified as being of sarcolemmal origin by enrichment of marker activities associated with the sarcolemma (e.g., binding of the ligands PN 200-110, iodocyanopindolol, and ouabain). The Vmax of Na-Ca exchange in the 2 aortic sarcolemmal prepns. (0.5-3.5 nmol/s/mg protein) is significantly higher than that previously reported with membrane prepns. derived from visceral and vascular smooth muscle, and compares favorably with maximal values recorded in cardiac sarcolemmal membrane vesicles (5-20 nmol/s/mg protein) under identical exptl. conditions. The Km of Ca2+ (15 μM) and the Km of Na+ (15 mM) are similar to those determined in heart. Aortic and cardiac Na-Ca exchange activities are equivalent in their sensitivity to inhibition by La3+ and 2 known classes of mechanism-based organic blockers of transport activity (i.e., amiloride analogs and bepridil-like agents). Both also display electrogenic behavior. However, Li+, K+, and choline all inhibit the smooth muscle transporter with markedly greater potency than found in heart, and intravesicular Ca2+ does not affect transport activity in smooth muscle membranes as it does in the cardiac system. When maximal transport velocities are compared, aortic membrane vesicles have 3-6-fold higher Na-Ca exchange than sarcolemmal Ca2+-ATPase Ca2+ transporting capacities. The ratio of these activities, and the specific activity of Na-Ca exchange in this tissue, suggests that Na-Ca exchange is a major pathway for mediating sarcolemmal Ca2+ flux in vascular smooth muscle.

IT 1166-01-4, 3',4'-Dichlorobenzamil
RL: BIOL (Biological study)
(calcium-sodium antiport by aorta smooth muscle sarcolemma membrane inhibition by)

RN 1166-01-4. CAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



L6 ANSWER 80 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1989:128071 CAPLUS

DOCUMENT NUMBER: 110:128071

TITLE: Inhibition of colonic sodium transport by amiloride analogs

AUTHOR(S): Bridges, Robert J.; Cragoe, Edward J., Jr.; Frizzell, Raymond A.; Benos, Dale J.

CORPORATE SOURCE: Dep. Physiol. Biophys., Univ. Alabama at Birmingham, Birmingham, AL, 35294, USA

SOURCE: American Journal of Physiology (1989), 256(1, Pt. 1), C67-C74
CODEN: AJPHAP; ISSN: 0002-9513

DOCUMENT TYPE: Journal

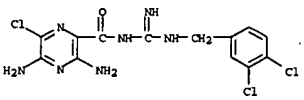
LANGUAGE: English

AB The ability of several amiloride analogs to inhibit electrogenic Na+ transport in colon from dexamethasone-treated rats was compared. Short-circuit current (Isc) across the colonic mucosa and 22Na+ uptake into membrane vesicles derived from colonic enterocytes were determined in dexamethasone-treated rats. Kinetic anal. of inhibition of Isc and 22Na+ uptake revealed the presence of a high- and low-affinity amiloride pathway. One pathway had a high affinity for benzamil, phenamil, 3',4'-dichlorobenzamil, and amiloride but a much lower affinity for 5-(N-ethyl-N-isopropyl)amilorideand 5-(N-propyl-N-butyl)-2',4'-dichlorobenzamil. The high-affinity pathway accounted for 75-83% of the transport of Na+. The 2nd pathway had nearly the same low affinity for each of the analogs and accounted for only 15-25% of the transport of Na+. The results demonstrate that the structure-inhibitory pattern of these amiloride analogs for the high-affinity pathway is the the same as that observed in other electrogenic Na+-transporting epithelia and that this pharmacol. profile is preserved in membrane vesicles derived from colonic enterocytes. These results suggest that apical membrane entry of Na+ is mediated by a Na+-H+ exchanger in the colon of normal rats.

IT 1166-01-4, 3',4'-Dichlorobenzamil 119648-51-0
RL: BIOL (Biological study)
(sodium transport by colon inhibition by, structure in relation to)

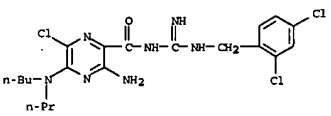
RN 1166-01-4 CAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



RN 119648-51-0 CAPLUS

CN Pyrazinecarboxamide, 3-amino-5-(butylpropylamino)-6-chloro-N-[[[(2,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



L6 ANSWER 81 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1989:92696 CAPLUS

DOCUMENT NUMBER: 110:92696

TITLE: Effects of dichlorobenzamil, a sodium-calcium exchange inhibitor, on the calcium paradox and the sodium withdrawal contractures of frog atrial muscle

AUTHOR(S): Suarez-Kurtz, G.; Sollero, T.; Leal-Cardoso, J. H.; Kaczorowski, G.

CORPORATE SOURCE: Dep. Farmacol., Univ. Fed. Rio de Janeiro, Rio de Janeiro, 21941, Brazil

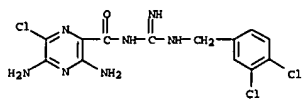
SOURCE: Brazilian Journal of Medical and Biological Research (1988), 21(6), 1197-211
CODEN: BJMRDK; ISSN: 0100-879X

DOCUMENT TYPE: Journal

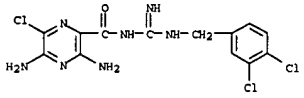
LANGUAGE: English

AB The effects of dichlorobenzamil (DCB), an amiloride derivative and potent inhibitor of Na-Ca exchange in cardiac sarcolemmal vesicles and isolated cardiac myocytes, were investigated in 2 paradigms involving Na-Ca exchange, namely the Ca2+ paradox and the Na+-withdrawal contractures of frog atrial muscle strips. Pretreatment with DCB (10-100 μM) inhibited in a concentration-dependent manner the contractures elicited by reexposure of the atrial strips to the control Ringer solution after a 5-20 min equilibration with a Ca2+-free saline (Ca2+-readmission contractures; Ca2+ paradox). These contractures were not inhibited, however, when DCB was applied after the preparation had been exposed to the Ca2+-free saline, but before the reexposure to the control Ringer solution. DCB (10-100 μM) did not inhibit the contractures elicited by Na+-deficient saline (Na+-withdrawal contractures) in atrial strips pretreated or not with acetylstrophantydin. Under these exptl. conditions, DCB failed to substantially inhibit the Ca2+ influx mediated by Na-Ca exchange. The duration of the plateau of the action potentials of atrial cells equilibrated with Ca2+-free saline was reduced from 1.42 s to 0.61 s by 50 μM DCB. This was attributed to blockade of Na+ currents through modified L-type Ca2+ channels. The shortening of the Na+-dependent action potentials can account for the inhibition of the Ca2+-readmission contractures, because these contractures have a steep dependence on the Na+ influx and intracellular Na+ accumulation that occurs during the Ca2+-free period. Thus, DCB has multiple effects on heart muscle, including a potent blockade of Ca2+ channels, and its use as a selective

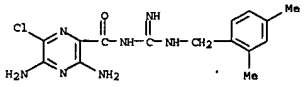
inhibitor of Na-Ca exchange in cellular systems is unwarranted.
IT 1166-01-4, Dichlorobenzamil
RL: BIOL (Biological study)
(calcium paradox and sodium withdrawal contracture of atrial muscle response to, as calcium-sodium exchange inhibitor)
RN 1166-01-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



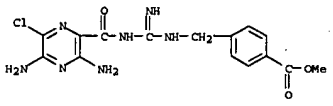
L6 ANSWER 82 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1989:53063 CAPLUS
DOCUMENT NUMBER: 110:53063
TITLE: Characterization of the mitochondrial sodium-proton exchange. The effect of amiloride analogs
AUTHOR(S): Kapus, Andras; Lukacs, Gergely L.; Cragoe, Edward J., Jr.; Ligeti, Erzsebet; Fonyo, Attila
CORPORATE SOURCE: Dep. Physiol., Semmelweis Med. Univ., Budapest, H-1444, Hung.
SOURCE: Biochimica et Biophysica Acta, Biomembranes (1988), 944(3), 383-90
CODEN: BBBMBS; ISSN: 0005-2736
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The kinetic properties and inhibitor sensitivity of the Na+-H+ exchange activity present in the inner membrane of rat heart and liver mitochondria were studied. Na+-induced H+ efflux from mitochondria followed Michaelis-Menten kinetics. In heart mitochondria, the Km for Na+ was 24 mM and the Vmax was 4.5 nmol H+/mg protein/s. Basically similar values were obtained in liver mitochondria (Km = 31 mM, Vmax = 5.3 nmol H+/mg protein/s). Li+ proved to be a substrate (Km = 5.9 mM, Vmax = 2.3 nmol H+/mg protein/s) and a potent competitive inhibitor with respect to Na+ (Ki = 0.7 mM). External H+ inhibited the mitochondrial Na+-H+ exchange competitively. Two benzamil derivs. of amiloride, 5-(N-4-chlorobenzyl)-N-(2',4'-dimethyl)benzamiland 3',5'-bis(trifluoromethyl)benzamil, were effective inhibitors of the mitochondrial Na+-H+ exchange (50% inhibition was attained by .apprx.60 μM in the presence of 15 mM Na+). Three 5-amino analogs of amiloride, which are very strong Na+-H+ exchange blockers on the plasma membrane, exerted only weak inhibitory activity on the mitochondrial Na+-H+ exchange. The results indicate that the mitochondrial and the plasma membrane antiporters represent distinct mol. entities.
IT 118573-60-7 118593-88-7
RL: BIOL (Biological study)
(proton-sodium antiport of mitochondrial membrane response to, plasma membrane antiport in relation to)
RN 118573-60-7 CAPLUS
CN Pyrazinecarboxamide, 3-amino-6-chloro-5-[[(4-chlorophenyl)methyl]amino]-N-[[[(2,4-dimethylphenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



RN 2093-13-2 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2,4-dimethylphenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



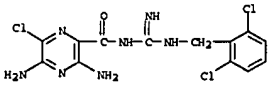
RN 117241-68-6 CAPLUS
CN Benzoic acid, 4-[[[[[(3,5-diamino-6-chloropyrazinyl)carbonyl]amino]iminomethyl]amino]methyl]-, methyl ester (9CI) (CA INDEX NAME)



RN 117241-70-0 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2,6-dichlorophenyl)methyl]amino]iminomethyl]-,compd. with N,N-dimethylformamide (2:1) (9CI) (CA INDEX NAME)

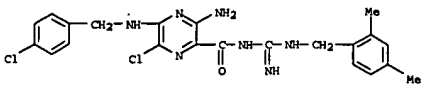
CM 1

CRN 117241-69-7
CMF C13 H12 Cl3 N7 O

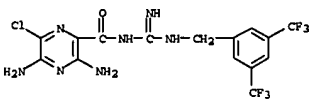


CM 2

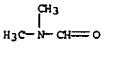
CRN 68-12-2
CMF C3 H7 N O



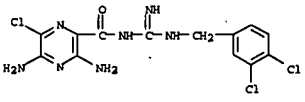
RN 118593-88-7 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-[[[[3,5-bis(trifluoromethyl)phenyl]methyl]amino]iminomethyl]-6-chloro-(9CI) (CA INDEX NAME)



L6 ANSWER 83 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1988:583053 CAPLUS
DOCUMENT NUMBER: 109:183053
TITLE: Amiloride analogs cause endothelium-dependent relaxation in the canine coronary artery in vitro: possible role of sodium/calcium exchange
AUTHOR(S): Cocks, T. M.; Little, P. J.; Angus, J. A.; Cragoe, E. J., Jr.
CORPORATE SOURCE: Baker Med. Res. Inst., Prahran, 3181, Australia
SOURCE: British Journal of Pharmacology (1988), 95(1), 67-76
CODEN: BJPCBM; ISSN: 0007-1188
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effect of amiloride analogs in endothelium-dependent relaxations were studied. The analogs used were those substituted on either the 5-amino group or the terminal guanidino nitrogen atom. The former block both Na+/Ca2+ and Na+/H+ exchange, while the latter block the Na+ channel and Na+/Ca2+ exchange. Both series of compds. caused relaxation in isolated rings of dog coronary artery (EC50 values, 1-10 μM), presumably due to release of endothelium-derived relaxing factor (EDRF), since removal of endothelium greatly attenuated the response. Amiloride (1-100 μM) had little effect on either endothelium-intact or denuded arteries. The guanidino-substituted analogs also appeared to block selectively the relaxation response to acetylcholine in the coronary artery, independently of their EDRF-releasing activity. It is proposed that endothelial cells have an active Na+/Ca2+ exchange operating in the forward mode to extrude Ca2+. This mechanism may be important in the control of EDRF release. Furthermore it may be possible to use selective amiloride analog clin. as antihypertensive drugs to relieve spasm in certain arteries such as the coronary and cerebral.
IT 1166-01-4 2093-13-2 117241-68-6 117241-70-0
RL: BIOL (Biological study)
(endothelium-dependent relaxation in coronary artery induction by, sodium/calcium exchange in, structure in relation to)
RN 1166-01-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



L6 ANSWER 84 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1988:524126 CAPLUS
DOCUMENT NUMBER: 109:124126
TITLE: Evidence for distinct sites coupled to high affinity ω-conotoxin receptors in rat brain synaptic plasma membrane vesicles
AUTHOR(S): Feigenbaum, Pamela; Garcia, Maria L.; Kaczorowski, Gregory J.
CORPORATE SOURCE: Dep. Membrane Biochem. Biophys., Merck Sharp and Dohme Research Lab., Rahway, NJ, 07065, USA
SOURCE: Biochemical and Biophysical Research Communications (1988), 154(1), 298-305
CODEN: BBRCA9; ISSN: 0006-291X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The neuronal Ca2+ channel blocker ω-conotoxin (GVIA) binds with very high affinity (Kd of 0.8 pM) to a single class of receptors in purified rat brain synaptic plasma membrane vesicles. Three types of agents have been found to modulate toxin binding. The affinity of ω-conotoxin is decreased by metal ions or organic cations which interact at the pore of voltage-dependent Ca2+ channels. Dynorphin A and related peptides stimulate ω-conotoxin binding by increasing toxin affinity through a nonopiate allosteric mechanism. Venom of the spider Plectreurys tristes inhibits ω-conotoxin binding (IC50 of 30 ng protein/mL) by a noncompetitive allosteric mechanism. Evidently ω-conotoxin binding sites exist in a complex with distinct receptors for other agents, all of which may be functionally associated with neuronal Ca2+ channels.
IT 1166-01-4
RL: BIOL (Biological study)
(receptors of brain synaptic vesicles for ω-conotoxin blockade by)
RN 1166-01-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



L6 ANSWER 85 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1988:504425 CAPLUS
DOCUMENT NUMBER: 109:104425
TITLE: Paradoxical effects of amiloride analogs on protein phosphorylation and serotonin release induced by agonists in human platelets
AUTHOR(S): Yoshida, Kenichi; Matoba, Ryoji; Cragoe, Edward J., Jr.; Nachmias, Vivianne T.
CORPORATE SOURCE: Med. Sch., Osaka Univ., Osaka, 530, Japan
SOURCE: Biochemical and Biophysical Research Communications (1988), 154(1), 101-7
CODEN: BBRCA9; ISSN: 0006-291X

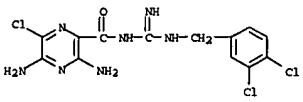
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effects of new amiloride analogs on protein phosphorylation and serotonin secretion induced by various agonists in human platelets was examined 3',4'-Dichlorobenzamil (DCB) and to a lesser extent, 2',4'-dimethylbenzamil (DMB), which in many cells are highly specific inhibitors of the Na+/Ca2+-pump, inhibited the phosphorylation of 47 K- and 20 K-dalton proteins and serotonin secretion in human platelets independently of the action on the pump. DCB also induced dephosphorylation of 47 K and 20 K after the phosphorylation of these proteins by thrombin and released serotonin by itself.

IT 1166-01-4, 3',4'-Dichlorobenzamil 2093-13-2
RL: BIOL (Biological study)
(protein phosphorylation and serotonin release by blood platelets of humans inhibition by)

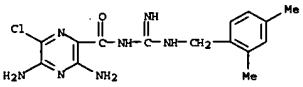
RN 1166-01-4 CAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



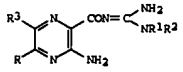
RN 2093-13-2 CAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2,4-dimethylphenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



L6 ANSWER 86 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1988:447850 CAPLUS
DOCUMENT NUMBER: 109:47850
TITLE: Phenamil, an amiloride analog, inhibits differentiation of Friend murine erythroleukemic cells
AUTHOR(S): Lannigan, Deborah A.; Bennington, J. Bret; Cragoe, E. J., Jr.; Knauf, Philip A.
CORPORATE SOURCE: Sch. Med. Dent., Univ. Rochester, Rochester, NY, 14642, USA
SOURCE: American Journal of Physiology (1988), 254(1, Pt. 1), C122-C129
CODEN: AJPHAP; ISSN: 0002-9513
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



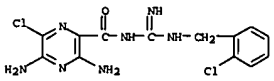
I

AB A series of amiloride analogs I (R = H, NH2, NMe2, NHCHMe2, NHCH2C6H4F-2; R1 = H, Me; R2 = H, Ph, CH2Ph, CH2C6H4Cl-2, etc.; R3 = halo) were screened to determine whether a more potent and specific inhibitor of MEL cell differentiation could be found. Amiloride itself did not inhibit MEL cell differentiation. However, the amiloride analog phenamil (I, R = NH2, R1 = H; R2 = Ph; R3 = Cl) (II) reversibly inhibited DMSO-induced MEL cell commitment to differentiate with a K1/2 of 2.5-5.0 μM (in the plasma clot assay). At an extracellular concentration of 15 μM, II inhibited the commitment to differentiate by .apprx.90% in the plasma clot assay while having a minimal effect on growth. II is not metabolized but is rapidly taken up by MEL cells. II was most effective as an inhibitor when present during the 1st 12 h of DMSO treatment, indicating that II affects the early commitment process rather than later steps involved in Hb synthesis. II does not, however, inhibit the early differentiation-induced decrease in [Na+]i and the concomitant drop in the Na+-K+ pump rate. A specific binding site for II is suggested because some analogs in which the II structure is slightly modified are unable to inhibit differentiation.

IT 1163-44-6F, 2'-Chlorobenzamil 1634-16-8F, 4'-Fluorobenzamil
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and erythroleukemia differentiation inhibition by, structure in relation to)

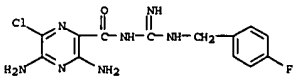
RN 1163-44-6 CAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2-chlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



RN 1634-16-8 CAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(4-fluorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



L6 ANSWER 87 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN

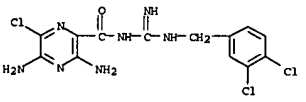
ACCESSION NUMBER: 1988:416601 CAPLUS
DOCUMENT NUMBER: 109:16601
TITLE: Effects of amiloride and its analogs on [3H]batrachotoxinin-A 20-α benzoate binding, [3H]tetracaine binding, and sodium-22 influx
AUTHOR(S): Velly, Jeanne; Grima, Michele; Decker, Nicole; Cragoe, Edward J., Jr.; Schwartz, Jean
CORPORATE SOURCE: Inst. Pharmacol., Fac. Med., Strasbourg, 67000, Fr.
SOURCE: European Journal of Pharmacology (1988), 149(1-2), 97-105
CODEN: EJPHAZ; ISSN: 0014-2999
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The ability of amiloride and its analogs to inhibit [3H]batrachotoxinin-A 20-α benzoate ([3H]BTX-B) and [3H]tetracaine binding to rat synaptosomes and to rat heart membrane prepns. was tested. Their ability to inhibit 22Na influx was determined with rat synaptosomes. The 5-N-substituted analogs were generally more potent in inhibiting [3H]BTX-B and [3H]tetracaine binding than compds. substituted on the guanidine group, but the inhibition was not competitive. Amiloride and some of its analogs were as active or more active in inhibiting [3]tetracaine binding than they were in inhibiting [3H]BTX-B binding. 22Na influx was inhibited with the same relative potencies as [3H]BTX-B binding and a pos. correlation was found between the 2 inhibitory activities. These results show an effect of amiloride and its analogs on the voltage-sensitive Na+ channels, which could partly explain the inotropic effects of these drugs.

IT 1166-01-4, 3',4'-Dichlorobenzamil
RL: BIOL (Biological study)
(batrachotoxinin A and tetracaine binding and sodium influx inhibition by, structure in relation to)

RN 1166-01-4 CAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



L6 ANSWER 88 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN

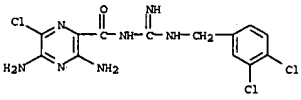
ACCESSION NUMBER: 1988:400541 CAPLUS
DOCUMENT NUMBER: 109:541
TITLE: Amiloride increases the sensitivity of particulate guanylate cyclase to atrial natriuretic factor
AUTHOR(S): Heim, Joerg Martin; Ivanova, Krassimira; Gerzer, Rupert
CORPORATE SOURCE: Med. Klin. Innenstadt, Univ. Muenchen, Munich, D-8000/2, Fed. Rep. Ger.
SOURCE: Biochemical and Biophysical Research Communications (1988), 152(3), 1263-8
CODEN: BBRCA9; ISSN: 0006-291X
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The natriuretic agent amiloride induced a shift of the dose-response curve of particulate guanylate cyclase of the bovine adrenal cortex to rat atrial natriuretic factor (99-126) (ANF) to the left. The ANF concentration for half-maximal activation of guanylate cyclase was shifted from 20 to 3 nM in the presence of 100 μM amiloride. This effect was observed with GTP-Mn2+, but not with GTP-Mg2+, as the substrate. Amiloride derivs., which inhibit a specific Na+-channel, also shifted the dose-response curve to the left. Apparently, some of the effects of amiloride are mediated by an increased sensitivity of particulate guanylate cyclase to ANF.

IT 1166-01-4
RL: BIOL (Biological study)
(guanylate cyclase stimulation by atriopeptin potentiation by, in adrenal cortex)

RN 1166-01-4 CAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



L6 ANSWER 89 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN

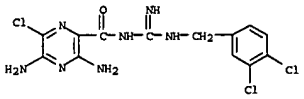
ACCESSION NUMBER: 1988:145550 CAPLUS
DOCUMENT NUMBER: 108:145550
TITLE: Inhibition of sodium-calcium exchange in cardiac sarcolemmal membrane vesicles. 1. Mechanism of inhibition by amiloride analogs
AUTHOR(S): Slaughter, Robert S.; Garcia, Maria L.; Cragoe, Edward J., Jr.; Reeves, John P.; Kaczorowski, Gregory J.
CORPORATE SOURCE: Dep. Biochem., Merck Inst. Ther. Res., Rahway, NJ, 07065, USA
SOURCE: Biochemistry (1988), 27(7), 2403-9
CODEN: BICHAW; ISSN: 0006-2960
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The mechanism by which terminal guanidino N-substituted analogs of amiloride inhibit Na-Ca exchange in purified cardiac sarcolemmal membrane vesicles was investigated. These inhibitors block both Nai-dependent (i = inside) Ca2+ uptake and Nao-dependent (o = outside) Ca2+ efflux. Inhibition of Na-Ca exchange monitored in K+ is noncompetitive vs. Ca2+ but competitive vs. Na+. Substitution of sucrose for K+ results in mixed kinetics of inhibition vs. Ca2+, suggesting a complex interaction between inhibitor and carrier under this condition. Amiloride derivs. also block 2 other modes of carrier action: Na-Na exchange is inhibited in a competitive fashion with Na+, and kinetics of Ca-Ca exchange inhibition are mixed vs. Ca2+ in either sucrose or K+. However, Ca-Ca exchange inhibition can be alleviated by increasing K+ concentration Dixon analyses of Na-Ca exchange block with mixts. of inhibitors suggest that these agents are interacting at >1 site. In addition, Hill plots of inhibition are biphasic with Hill coeffs. of 1 and 2 at low and high inhibitor concns., resp. These results indicate that amiloride derivs. are mechanism-based inhibitors that interact at 2 classes of substrate-binding sites on the carier; at low concentration they bind preferentially to a site that is exclusive for Na+, whereas at higher concentration they also interact at a site that is common for Na+, Ca2+, and K+.

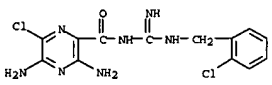
IT 1166-01-4, 3',4'-Dichlorobenzamil
RL: BIOL (Biological study)
(calcium-sodium exchange by heart sarcolemma membrane vesicles inhibition by, mechanism of)

RN 1166-01-4 CAPLUS

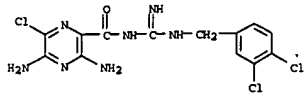
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



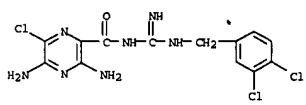
L6 ANSWER 90 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1988:124214 CAPLUS
DOCUMENT NUMBER: 108:124214
TITLE: Effects of N-chlorobenzyl analogs of amiloride on myocardial contractility, sodium-calcium exchange carrier and other cardiac enzymic activities
AUTHOR(S): Floreani, M.; Tessari, M.; Debetto, P.; Luciani, S.; Carpenedo, F.
CORPORATE SOURCE: Dip. Farmacol., Univ. Padova, Padua, I-35131, Italy
SOURCE: Naunyn-Schmiedeberg's Archives of Pharmacology (1987), 336(6), 661-9
CODEN: NSAPCC; ISSN: 0028-1298
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To confirm the possibility that the in vitro observed pos. inotropic effect of amiloride could result from inhibition of the Na-Ca-exchange carrier, the cardiac effects of 2 potent inhibitors of Na-Ca-exchange carrier, o-chlorobenzamil and 3',4'-dichlorobenzamil, N-chlorobenzyl analogs of amiloride, in isolated guinea pig atria and in right ventricular papillary muscle were examined Both o-chlorobenzamil and 3',4'-dichlorobenzamil exerted a pos. inotropic effect on myocardial prepns. In addition, o-chlorobenzamil inhibited the pos. inotropic response induced by ouabain and prevented the rise in the resting force induced by the cardiac glycosides. Whereas 3',4'-dichlorobenzamil inhibited several enzyme systems involved in cardiac contractility, o-chlorobenzamil mainly blocked Na-Ca-exchange carrier and cAMP-dependent phosphodiesterase. Thus, N-chlorobenzyl derivs. of amiloride are compds. with important effects on several cellular systems involved in cardiac contractility.
IT 1163-44-6, o-Chlorobenzamil 1166-01-4
RL: BIOL (Biological study)
(heart contraction response to, calcium and sodium transport and enzymes in relation to)
RN 1163-44-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2-chlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



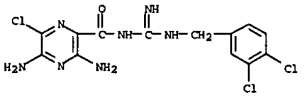
RN 1166-01-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



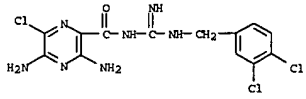
L6 ANSWER 91 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1988:87849 CAPLUS
DOCUMENT NUMBER: 108:87849
TITLE: Dichlorobenzamil inhibits stimulated bone resorption in vitro
AUTHOR(S): Krieger, Nancy S.; Kim, Sang Geon
CORPORATE SOURCE: Med. Sch., Northwestern Univ., Chicago, IL, 60611, USA
SOURCE: Endocrinology (1988), 122(2), 415-20
CODEN: ENDOAO; ISSN: 0013-7227
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effect of 3',4'-dichlorobenzamil (DCB) on basal and stimulated bone resorption from neonatal mouse calvaria in vitro was characterized. DCB inhibition of resorption from bones stimulated with 1 nM parathyroid hormone PTH was dose dependent. The 50% inhibitory concentration was about 7 μM, and complete inhibition occurred at 10 μM. DCB alone inhibited basal Ca release at 10 μM. Amiloride, which is less potent as an inhibitor of Na-Ca exchange, had no effect on PTH-stimulated resorption at concns. lower than 0.1 mM, but inhibited basal resorption at 10 μM. Stimulated Ca release was inhibited either by continuous treatment with DCB plus PTH for 72 h or by a short pretreatment with DCB alone, followed by removal of DCB before addition of PTH. At least 9-h pretreatment with DCB was necessary to block the subsequent response to PTH. The inhibitory effect of DCB pretreatment could be prevented if PTH was present together with DCB during pretreatment periods of 24 h or less. This reversibility suggests that the inhibition by DCB is not simply a toxic effect of the drug. DCB also inhibited resorption stimulated by 1,25-dihydroxyvitamin D3 or prostaglandin E2, which indicates that the effect of DCB is beyond the level of specific hormone-receptor interaction. Thus, the data are consistent with a role for Na-Ca exchange in the process of hormonally stimulated bone resorption.
IT 1166-01-4, 3',4'-Dichlorobenzamil
RL: BIOL (Biological study)
(bone resorption inhibition by, calcium-sodium exchange in)
RN 1166-01-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



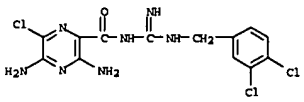
L6 ANSWER 92 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1988:53536 CAPLUS
DOCUMENT NUMBER: 108:53536
TITLE: A derivative of amiloride blocks both the light-regulated and cyclic GMP-regulated conductances in rod photoreceptors
AUTHOR(S): Nicol, G. D.; Schnetkamp, P. P. M.; Saimi, Y.; Cragoe, E. J., Jr.; Bownds, M. D.
CORPORATE SOURCE: Dep. Zool., Univ. Wisconsin, Madison, WI, 53706, USA
SOURCE: Journal of General Physiology (1987), 90(5), 651-69
CODEN: JGPLAD; ISSN: 0022-1295
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Vertebrate rod photoreceptors in the dark maintain an inward current across the outer segment membrane. The photoresponse results from a light-induced suppression of this dark current. The light-regulated current is not sensitive to either tetrodotoxin or amiloride, potent blockers of Na+ channels. A derivative of amiloride, 3',4'-dichlorobenzamil (DCPA), completely suppresses the dark current and light response recorded from rod photoreceptors. DCPA also blocks a cGMP-activated current in excised patches of rod plasma membrane and a cGMP-induced Ca2+ flux from rod disk membranes. These results are consistent with the notion that the Ca2+ flux mechanism in the disk membrane and the light-regulated conductance in the plasma membrane are identical. DCPA also inhibits the Na/Ca exchange mechanism in intact rods, but at a 5-10-fold higher concentration
than is required to block the cGMP-activated flux and current. The blocking action of DCPA in 10 nM Ca2+ is different from that in 1 mM Ca2+, which suggests either that the conductance state of the light-regulated channel may be modified in high and low concns. of Ca2+, or that there may be 2 ionic channels in the rod outer segment membrane.
IT 1166-01-4, 3',4'-Dichlorobenzamil
RL: BIOL (Biological study)
(calcium and sodium transport by eye rod outer segment in response to cGMP and light inhibition by)
RN 1166-01-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



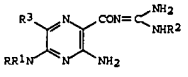
L6 ANSWER 93 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1987:590616 CAPLUS
DOCUMENT NUMBER: 107:190616
TITLE: Inhibition by amiloride analogs of sodium-dependent hexose uptake in LLC-PK1/C14 cells
AUTHOR(S): Cook, John S.; Shaffer, Carolyn; Cragoe, Edward J., Jr.
CORPORATE SOURCE: Biol. Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37831, USA
SOURCE: American Journal of Physiology (1987), 253(2, Pt. 1), C199-C204
CODEN: AJPHAP; ISSN: 0002-9513
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Amiloride and 4 analogs of amiloride were shown to inhibit Na+-dependent, phlorizin-sensitive hexose uptake by a clone of pig kidney cells, LLC-PK1/C14. The analogs tested were: 5-(N-ethyl-N-isopropyl)amiloride(EIPA), 5-(N-methyl-N-isobutyl)amiloride(MIBA), 3',4'-dichlorobenzamil, and phenamil. The transport substrate was the nonmetabolizable glucose analog α-methyl-D-glucoside. Blockade of Na+-K+ transport at the basolateral membranes or removal of divalent cations from the assay medium had little effect on the initial rate of hexose uptake, whereas MIBA remained an effective inhibitor under both conditions. The inhibitions by EIPA of Na+-H+ exchange and hexose-dependent Na+ uptake could be distinguished by appropriate choice of concns. of the inhibitor. Hexose transport inhibition does not appear to be secondary to other known effects of the amilorides. Inhibition by all analogs is enhanced when they are tested in low (2 mM) Na+ medium, where they show half-maximal inhibition in the range of 100-300 μM. More detailed kinetic anal. of inhibition by EIPA shows it to be competitive with Na+ with a Ki of 73-107 μM. Thus, the amilorides are acting directly on the hexose transporter.
IT 1166-01-4, 3',4'-Dichlorobenzamil
RL: BIOL (Biological study)
(sodium-dependent hexose uptake in kidney cells inhibition by)
RN 1166-01-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



L6 ANSWER 94 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1987:547084 CAPLUS
DOCUMENT NUMBER: 107:147084
TITLE: Amiloride derivatives that block sodium/calcium exchange inhibit spontaneous inward currents in sodium-loaded cardiac myocytes
AUTHOR(S): Cragoe, E.; Ravens, Ursula; Wettwer, E.
CORPORATE SOURCE: Pharmakol. Inst., Univ./Gesamthochsch. Essen, Essen, D-43/1, Fed. Rep. Ger.
SOURCE: European Journal of Pharmacology (1987), 140(1), 113-16
CODEN: EJPHAZ; ISSN: 0014-2999
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Spontaneous elec. and mech. activity was observed when single myocytes from guinea-pig hearts were loaded with Na+ by direct intracellular application. Transient membrane depolarizations were found to be due to spontaneous inward currents (Isp). Both Isp and spontaneous contractions were abolished by 2',3'-benzobenzamil or 3',4'-dichlorobenzamil, two compds. that were previously reported to inhibit Na+/Ca2+ exchange. These findings suggest that the spontaneous membrane currents in Na+-loaded myocytes could be generated by the Na+/Ca2+ exchange mechanism.
IT 1166-01-4, 3',4'-Dichlorobenzamil
RL: BIOL (Biological study)
(calcium-sodium exchange inhibition by, in heart)
RN 1166-01-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)

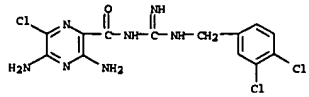


L6 ANSWER 95 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1987:470266 CAPLUS
DOCUMENT NUMBER: 107:70266
TITLE: Effect of amiloride analogs on sodium transport in toad bladder membrane vesicles. Evidence for two electrogenic transporters with different affinities toward pyrazinecarboxamides
AUTHOR(S): Asher, Carol; Cragoe, Edward J., Jr.; Garty, Haim
CORPORATE SOURCE: Dep. Membr. Res., Weizmann Inst. Sci., Rehovot, 72100, Israel
SOURCE: Journal of Biological Chemistry (1987), 262(18), 8566-73
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



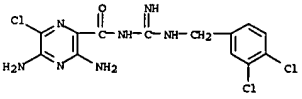
I

AB Most of the elec. potential-driven 22Na+ uptake in toad bladder membrane vesicles can be blocked by the diuretic amiloride. Anal. of the amiloride inhibition curve indicates the presence of 2 pathways with low and high affinities to the diuretic. The selectivity of these pathways to amiloride was explored by comparing the inhibition curve of this diuretic with those of 10 of its structural analogs I (R and R1 = H or alkyl; R2 = H, Ph, 2,4-chlorophenylmethyl, α-naphthylmethyl; R3 = Cl, F, I, Ph). The relative potencies of various amiloride-like compds. as blockers of the flux component with high affinity to amiloride were in good agreement with the structure-activity relations elucidated from transepithelial short-circuit current measurements. Thus, this pathway is most probably the apical Na+-specific channel. The other pathway with lower affinity to the diuretic was relatively insensitive to modifications of the amiloride mol., and the structure-activity relations measured for the inhibition of this pathway were different from those reported for any other amiloride-blockable process. Other expts. have established that the Na+ flux with low affinity to amiloride is electrogenic and is not mediated by a Na+/H+ or Na+/Ca2+ exchanger, Na+-hexose cotransporter, or the Na+/K+-ATPase. Thus, tracer flux measurements in toad bladder membrane vesicles monitor, in addition to the well-characterized apical Na+ channels, another amiloride-blockable electrogenic Na+ transporter. This pathway could be responsible for the basolateral amiloride-blockable Na+ conductance recently observed in nystatin-treated bladders.
IT 1166-01-4
RL: BIOL (Biological study)
(sodium uptake by bladder membrane vesicles inhibition by, structure in relation to)
RN 1166-01-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



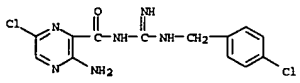
L6 ANSWER 96 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1987:456564 CAPLUS
DOCUMENT NUMBER: 107:56564
TITLE: Membrane electrical properties of vesicular sodium-calcium exchange inhibitors in single atrial myocytes
AUTHOR(S): Bielefeld, David R.; Hadley, Robert W.; Vassilev, Peter M.; Hume, Joseph R.
CORPORATE SOURCE: Dep. Pharmacol. Toxicol., Michigan State Univ., East Lansing, MI, 48824, USA
SOURCE: Circulation Research (1986), 59(4), 381-9
CODEN: CIRUAL; ISSN: 0009-7330
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Na+-loading single frog atrial cells produce changes in membrane currents that are similar to the creep currents originally observed in Na+-loaded cardiac Purkinje fibers. Exposure to the Na+ ionophore, monensin, was used to induce creep currents in isolated atrial cells. The sensitivity of myocardial creep currents to 3 compds. that have been shown to be inhibitors of Na+-Ca2+ exchange flux activity in isolated sarcolemmal vesicles was assessed. Dodecylamine, quinacrine, and the amiloride analog, 3',4'-dichlorobenzamil block creep currents at concns. well below those required to block Na+-dependent Ca2+ uptake in sarcolemmal vesicles. The estimated Kis for inhibition of myocardial creep currents were 3 μM for dodecylamin, 10 μm for quinacrine, and 4 μM for 3',4'-dichlorobenzamil. The sensitivity of creep currents to these compds. is consistent with the hypothesis that creep currents may represent the electrogenic activity of a Na+-Ca2+-exchange carrier. In an addnl. series of expts., the relative specificity of these compds. was tested by examining their effects on myocardial membrane channels. Both dodecylamine and 3',4'-dichlorobenzamil inhibited myocardial Ca2+ and K+ currents over the same range of concns. in which block of exchange activity occurs. These results seriously question the use of these exchange carrier inhibitors as selective exptl. probes for defining the role of Na-Ca exchange in various physiol. processes.
IT 1166-01-4
RL: BIOL (Biological study)
(calcium-sodium electrogenic exchange and calcium and potassium channel-mediated transport by heart atrium inhibition by)
RN 1166-01-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



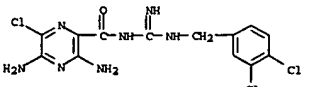
L6 ANSWER 97 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1987:432601 CAPLUS
DOCUMENT NUMBER: 107:32601
TITLE: Structure-activity relationship of amiloride analogs as blockers of epithelial sodium channels: II. Side-chain modifications
AUTHOR(S): Li, J. H. Y.; Cragoe, E. J., Jr.; Lindemann, B.
CORPORATE SOURCE: 2nd Dep. Physiol., Univ. Saarland, Homburg/Saar, 6650, Fed. Rep. Ger.
SOURCE: Journal of Membrane Biology (1987), 95(2), 171-85
CODEN: JMBBBO; ISSN: 0022-2631
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The overall on- and off-rate consts. for blockage of epithelial Na channels by amiloride analogs were estimated by noise anal. of the stationary Na current transversing frog skin epithelium. The (2-position) side chain structure of amiloride was varied in order to obtain structure/rate-constant relationships. Hydrophobic chain elongations [benzamil and related compds. of high blocking potency] increase the stability of the blocking complex (lowered off-rate), explained by attachment of the added Ph moiety to a hydrophobic area near the site of side chain interaction with the channel protein. Some other chain modifications show that the on-rate, which is smaller than a diffusion-limited rate, varies with side chain structure. In several cases this effect is not attributable to steric hindrance on encounter, which implies that the side chain interacts briefly with the channel protein (encounter complex) before the main blocking position of the mol. is attained. The encounter complex must be labile, since the overall rate consts. of blockage are not concentration-dependent. In 2 cases, changes at the 2-position side chain and at other ring ligands, with known effects on the blocking rate consts., could be combined in 1 analog. The rate consts. of blocking by the resulting compds. indicate that the structural changes have additive effects in terms of activation energies. Along with other observations (voltage dependence on the rate consts. and competition with the transported Na ion), these results suggest a blocking process of at least 2 steps. It appears that initially the 2-position side chain invades the outward-facing channel entrance, establishing a labile complex. Then the mol. is either released completely (no block) or the 6-ligand of the pyrazine ring gains access to its receptor counterpart, thus establishing the blocking complex, the lifetime of which is strongly determined by the electronegativity of the 6-ligand.
IT 108940-87-0P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and sodium ion channels in epithelium blockade by, structure in relation to)
RN 108940-87-0 CAPLUS
CN Pyrazinecarboxamide, 3-amino-6-chloro-N-[[[(4-chlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



L6 ANSWER 98 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1987:417833 CAPLUS
DOCUMENT NUMBER: 107:17833
TITLE: The actions of diazepam and diphenylhydantoin on fast and slow calcium uptake processes in guinea pig cerebral cortex synaptosomes
AUTHOR(S): Rampe, D.; Ferrante, J.; Triggle, D. J.
CORPORATE SOURCE: Sch. Pharm., State Univ. New York, Buffalo, NY, 14260, USA
SOURCE: Canadian Journal of Physiology and Pharmacology (1987), 65(4), 538-43
CODEN: CJPPAJ; ISSN: 0008-4212
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The activities of diazepam and diphenylhydantoin as inhibitors of the fast and slow phases of 45Ca2+ uptake in response to K+ depolarization and of [3H]nitrendipine binding were examined in guinea pig cerebral cortex synaptosomes. The slow phase of 45Ca2+ uptake was abolished in Na+-free media (choline substitution) and was more sensitive to inhibition by 3,4-dichlorobenzamil and represents a Na+-dependent Ca2+ uptake process. The fast component of uptake represents activation of voltage-dependent Ca2+ channels. Diazepam (to 300 μM) was selectively active against the fast component of 45Ca2+ uptake. The benzodiazepines Ro 11-3624 and Ro 11-3128 were similarly selective with a model stereoselectivity against the fast component of 45Ca2+ uptake. Diphenylhydantoin (100 and 200 μM) blocked nonselectively both fast and slow phases of Ca2+ uptake. Diazepam (60 μM) and diphenylhydantoin (200 μM) blocked [3H]nitrendipine binding in a competitive manner. Diazepam and diphenylhydantoin probably exert at least part of their anticonvulsant activity by inhibition of voltage-dependent Ca2+ channels.
IT 1166-01-4
RL: BIOL (Biological study)
(calcium uptake by cerebral cortex synaptosomes inhibition by)
RN 1166-01-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



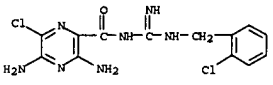
L6 ANSWER 99 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1987:188734 CAPLUS
DOCUMENT NUMBER: 106:188734
TITLE: Inhibition of cardiac phosphodiesterases by amiloride and its N-chlorobenzyl analogs
AUTHOR(S): Carpenedo, Francesca; Debetto, Patrizia; Floreani, Maura; Guarnieri, Adriano; Luciani, Sisto

CORPORATE SOURCE: Dep. Pharmacol., Univ. Padova, Padua, 35131, Italy
SOURCE: Biochemical Pharmacology (1987), 36(5), 778-80
CODEN: BCPCA6; ISSN: 0006-2952
DOCUMENT TYPE: Journal
LANGUAGE: English

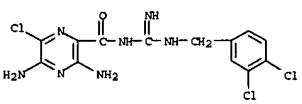
AB The o-chlorobenzyl [1163-44-6] and 3',4'-dichlorobenzyl [1166-01-4] derivs. of amiloride [2609-46-3] were good inhibitors of bovine heart cAMP phosphodiesterase [9036-21-9] and cGMP phosphodiesterase [9068-52-4]; whereas millimolar concns. of amiloride inhibited the enzymes, only micromolar amts. of the derivs. were required for inhibition. The cAMP-hydrolyzing enzyme was more sensitive to the inhibitors than the cGMP enzyme; the kinetics of cAMP phosphodiesterase inhibition were non-competitive.

IT 1163-44-6 1166-01-4
RL: BIOL (Biological study)
(cAMP and cGMP phosphodiesterases of heart inhibition by)

RN 1163-44-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2-chlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



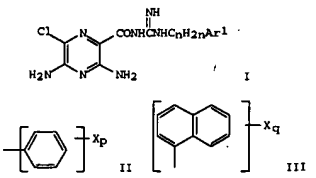
RN 1166-01-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



L6 ANSWER 100 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1986:583969 CAPLUS
DOCUMENT NUMBER: 105:183969
TITLE: Antiarrhythmic compositions and method
INVENTOR(S): Kaczorowski, Gregory J.; Siegl, Peter K. S.
PATENT ASSIGNEE(S): Merck and Co., Inc. , USA
SOURCE: U.S., 7 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 4604394	A	19860805	US 1984-655777	19841001
ZA 8507474	A	19860528	ZA 1985-7474	19850927
PRIORITY APPLN. INFO.:			US 1984-655777 A	19841001

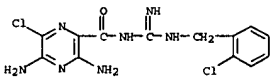
OTHER SOURCE(S): MARPAT 105:183969
GI



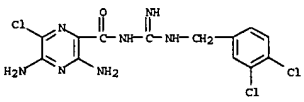
AB A method for treating cardiac arrhythmias is described which comprises administering to a subject a pyrazinoylguanidine compound I (Ar' = II, III; each X independently = halo, lower alkyl, lower alkoxy, NO2; p = 1-3; q = 0-2; n = 1, 2) or pharmaceutically acceptable salts thereof. Thus, the antiarrhythmic activity of 1-(3,5-diamino-6-chloropyrazine-2-carbonyl)-3-(3,4-dichlorobenzyl)guanidinewas demonstrated in vitro using papillary muscles isolated from the right ventricle of guinea pig hearts.

IT 1163-44-6 1166-01-4 2093-13-2
RL: BIOL (Biological study)
(as antiarrhythmic)

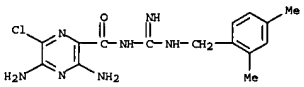
RN 1163-44-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2-chlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



RN 1166-01-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



RN 2093-13-2 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2,4-dimethylphenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)

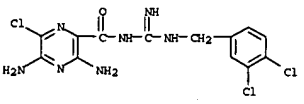


L6 ANSWER 101 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1986:545910 CAPLUS
DOCUMENT NUMBER: 105:145910
TITLE: Inhibition of multiple trans-sarcolemmal cation flux pathways by dichlorobenzamil in cultured chick heart cells
AUTHOR(S): Kim, Donghee; Smith, Thomas W.
CORPORATE SOURCE: Harvard Med. Sch., Brigham and Women's Hosp., Boston, MA, 02115, USA
SOURCE: Molecular Pharmacology (1986), 30(2), 164-70
CODEN: MOPMA3; ISSN: 0026-895X
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In cultured chick heart cells, dichlorobenzamil [1166-01-4] produced concentration-dependent decreases in the amplitude of cell motion, in Ca influx via Na-Ca exchange and slow Ca channels, and in Ca efflux via the sarcolemmal Ca pump. Dichlorobenzamil also inhibited Na pump activity and elevated cellular Na content. Results indicate that dichlorobenzamil has several sites of action in intact heart cells and that the neg. inotropic action of the drug is due, in part, to inhibition of Ca influx via both Na-Ca exchange and slow Ca channels.

IT 1166-01-4
RL: BIOL (Biological study)
(transsarcolemmal cation flux pathways inhibition by, in heart cells, neg. isotropic action in relation to)

RN 1166-01-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)

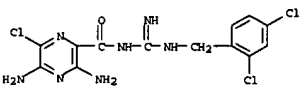


L6 ANSWER 102 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1986:49253 CAPLUS
DOCUMENT NUMBER: 104:49253
TITLE: The sodium/hydrogen exchange system in cardiac cells: its biochemical and pharmacological properties and its role in regulating internal concentrations of sodium and internal pH
AUTHOR(S): Lazdunski, Michel; Frelin, Christian; Vigne, Paul
CORPORATE SOURCE: Cent. Biochim., Fac. Sci., Nice, 06034, Fr.
SOURCE: Journal of Molecular and Cellular Cardiology (1985), 17(11), 1029-42
CODEN: JMCDAY; ISSN: 0022-2828
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Properties of the amiloride-sensitive Na+/H+ antiporter in chick cardiac cells are compared with those in other cellular systems and the role of the Na+/H+ exchanger in the regulation of internal Na+ concns. and internal pH is analyzed. Among the different properties are: (1) the external Na+ concentration ([Na+]0) dependence: the activity increases when [Na+]0 increases; (2) the external pH (pH0) dependence: the activity of the exchanger increases when pH0 increases; (3) the internal pH (pHi) dependence: the activity of the exchanger increases in a cooperative way when pHi decreases; (4) there are derivs. of amiloride which are 200 times more potent than amiloride itself and which are selective on the Na+/H+ exchange system vs. other Na+ transporting systems including the Na+/Ca2+ exchange system. Under physiol. conditions, the Na+/N+ exchange system contributes little to the regulation of the pHi of chick cardiac cells. It then serves as an uptake system for Na+ using the H+ gradient created by other pHi regulatory mechanisms. Treatment of cardiac cells with ouabain inhibits Na+ efflux and produces an increase in intracellular Na+ activity. Ethylisopropylamilorideas used to show that the Na+/H+ exchanger system is the main pathway for Na+ entry and accumulation in digitalis action. Amiloride deriva. which block Na+ entry via the Na+/H+ antiporter antagonize ouabain action on cardiac cell. At lowered pHi, the Na+/H+ exchanger becomes the major pHi regulating system, due to an increased activity at acidic pHi and to a decreased activity of other pHi regulatory systems. The Na+/H+ exchange system may play a key role in Na+ accumulation followed by Ca2+ accumulation which is observed when ischemic hearts are reperfused.

IT 90689-42-2
RL: BIOL (Biological study)
(proton-sodium exchange inhibition by, in heart)

RN 90689-42-2 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



L6 ANSWER 103 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1985:612338 CAPLUS
DOCUMENT NUMBER: 103:212338
TITLE: Phenamil: an irreversible inhibitor of sodium channels in the toad urinary bladder
AUTHOR(S): Garvin, Jeffrey L.; Simon, Sidney A.; Cragoe, Edward J., Jr.; Mandel, Lazaro J.
CORPORATE SOURCE: Med. Cent., Duke Univ., Durham, NC, 27710, USA
SOURCE: Journal of Membrane Biology (1985), 87(1), 45-54
CODEN: JMBBBO; ISSN: 0022-2631
DOCUMENT TYPE: Journal
LANGUAGE: English

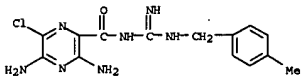
AB Several new amiloride analogs and 2 reported photoaffinity analogs were tested for irreversible inhibition of short-circuit current, Ksc, in toad (Bufo marinus) bladder. Bromoamiloride, a photoaffinity analog, induced 40% irreversible inhibition at 500 μM after irradiation with UV light ≥320 nm. Iodoamiloride caused no irreversible inhibition. Of the new analogs tested, only 3,5-diamino-6-chloro-N-[(phenylamino)aminomethylene] pyrazinecarboxamide (phenamil), irreversibly inhibited Isc at concns. of 0.05-5 μM when added to the mucosal solution Irreversible inhibition of Ixc by phenamil may be attributed to specific blockage of the mucosal Na+ channels, which depended on: (1) time of exposure; (2) mucosal pH; and, (3) mucosal Na+ concentration For example, 5-μM phenamil

irreversibly inhibited Isc by 38% in 103 mM Na+ at pH 8.6 and nearly 75% in 30 mM Na+ at pH 6.4 after a 40-min exposure. Irreversible inhibition occurred in 2 phases with time consts. of ≤10 min and .apprx.140 min. Due to its irreversible nature, phenamil may be used to measure channel d.

IT 1163-45-7
RL: BIOL (Biological study)
(sodium channels of bladder epithelium inhibition by)

RN 1163-45-7 CAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[(4-methylphenyl)methyl]amino]methyl]-(9CI) (CA INDEX NAME)



L6 ANSWER 104 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1985:142791 CAPLUS

DOCUMENT NUMBER: 102:142791

TITLE: Inhibition of sodium-calcium exchange in pituitary plasma membrane vesicles by analogs of amiloride

AUTHOR(S): Kaczorowski, Gregory J.; Barros, Francisco; Dethmers, Judy K.; Trumble, Mayme J.; Cragoe, Edward J., Jr.

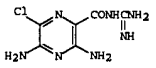
CORPORATE SOURCE: Dep. Biochem., Merck Inst. Ther. Res., Rahway, NJ, 07065, USA

SOURCE: Biochemistry (1985), 24(6), 1394-403
CODEN: BICHAW; ISSN: 0006-2960

DOCUMENT TYPE: Journal

LANGUAGE: English

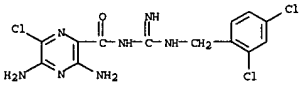
GI



I

AB Amiloride (I) [2609-46-3] is a weak inhibitor of Na+/Ca2+ exchange in isolated plasma membrane vesicles prepared from GH3 rat anterior pituitary cells. However, substitution on either a terminal guanidino N atom or the 5-amino N atom can increase inhibitory potency approx. 100-fold (I50 .apprx. 10 μM). Defined structural modifications of guanidino substituents are associated with increases in inhibitory activity. In contrast, I analogs bearing 5-amino substituents generally increase in potency with increasing hydrophobicity of the substitution. Specificity in action of either class is indicated by several criteria. These inhibitors do not disrupt the osmotic integrity of the membrane, nor do they significantly interfere with plasmalemmal Ca2+-ATPase-driven Ca2+ uptake, Na+,K+-ATPase enzymic activity, or the function of Ca2+ or K+ channels. Inhibition is freely reversible, further indicating a lack of nonspecific membrane effects. The mechanism by which each inhibitor class blocks exchange was identical. Protonation of the guanidino moiety (i.e., cationic charge) is essential for activity. Anal. of transport inhibition as a function of Ca2+ concentration indicates noncompetitive kinetics. However,

CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



L6 ANSWER 105 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1984:465550 CAPLUS

DOCUMENT NUMBER: 101:65550

TITLE: Inhibition of sodium/calcium exchange in membrane vesicle and papillary muscle preparations from guinea pig heart by analogs of amiloride

AUTHOR(S): Siegl, P. K. S.; Cragoe, E. J., Jr.; Trumble, M. J.; Kaczorowski, G. J.

CORPORATE SOURCE: Merck Inst. Ther. Res., West Point, PA, 19486, USA

SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1984), 81(10), 3238-42
CODEN: PNASA6; ISSN: 0027-8424

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Na+-Ca2+ exchange is inhibited in both guinea pig cardiac membrane vesicles and papillary muscles in a concentration-dependent fashion by several analogs of the pyrazine diuretic amiloride. Structure-activity studies based on transport measurements in vesicles prepared from guinea pig left ventricle indicate that hydrophobic substitutions at the terminal N atoms of the guanidinium moiety of amiloride improved the inhibitory potency almost 100-fold over that of the parent compound 3',4'-Dichlorobenzamil (DCB) [91235-36-6] is one of the most active inhibitors (IC50 = 17 μM). In elec. stimulated papillary muscles isolated from guinea pig heart, 10-40 μM DCB decreases contractile force. At 100 μM inhibitor, diastolic tension is increased. The pos. inotropic responses to veratridine and ouabain are inhibited by 20 and 40 μM DCB. Since the responses to these interventions were a consequence of increased intracellular Na+ concentration, these data indicate that DCB is an inhibitor of Na+-dependent Ca2+ influx in the intact tissue. Interpretation of mech. responses elicited by paired pulses suggests that 40 μM but not 100 μM DCB decreases release of Ca2+ from the sarcoplasmic reticulum. The mech. data obtained with concns. of DCB that inhibited Na+-Ca2+ exchange in vesicles suggest that a significant amount of Ca2+ can enter the cardiac cell via Na+-Ca2+ exchange under normal conditions and that this transport system may be an important source of Ca2+ supplying the sarcoplasmic reticulum in guinea pig heart. Moreover, these amiloride analogs function as potent inhibitors of the pos. inotropic effect caused by increased intracellular Na+ concentration

IT 1163-44-6 1166-01-4 2093-13-2
RL: BIOL (Biological study)
(calcium-sodium exchange in heart membrane vesicle and capillary muscle response to, structure in relation to)

RN 1163-44-6 CAPLUS

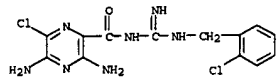
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2-chlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)

inhibition was reversed by elevating intravesicular Na+, indicating a competitive interaction with this ion. Apparently, the inhibitors function as Na+ analogs, interact at a Na+ binding site on the carrier (presumably the site at which the third Na+ binds), and reversibly tie up the transporter in an inactive complex. In addition to blocking pituitary exchange, the I analogs are also effective inhibitors of the bovine brain and porcine cardiac transport systems.

IT 1163-44-6 1163-45-7 1166-01-4 2093-13-2 90689-42-2
RL: BIOL (Biological study)
(calcium-sodium exchange by pituitary inhibition by)

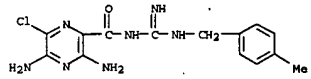
RN 1163-44-6 CAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2-chlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



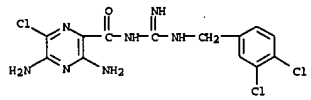
RN 1163-45-7 CAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[(4-methylphenyl)methyl]amino]methyl]-(9CI) (CA INDEX NAME)



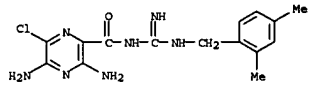
RN 1166-01-4 CAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)

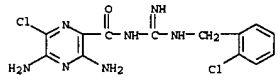


RN 2093-13-2 CAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2,4-dimethylphenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)

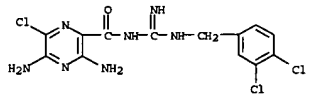


RN 90689-42-2 CAPLUS



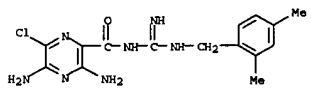
RN 1166-01-4 CAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



RN 2093-13-2 CAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2,4-dimethylphenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



L6 ANSWER 106 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1984:416649 CAPLUS

DOCUMENT NUMBER: 101:16649

TITLE: Amiloride and other blockers of electrolyte flux as inhibitors of progesterone-stimulated meiotic maturation in Xenopus oocytes

AUTHOR(S): Cameron, Ivan L.; Lum, Jean B.; Cragoe, Edward J., Jr.

CORPORATE SOURCE: Health Sci. Cent., Univ. Texas, San Antonio, TX, 78284, USA

SOURCE: Cell and Tissue Kinetics (1984), 17(2), 161-9
CODEN: CTKIAR; ISSN: 0008-8730

DOCUMENT TYPE: Journal

LANGUAGE: English

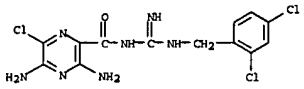
AB The progesterone-stimulated Xenopus laevis oocyte maturation system was tested as a convenience system to screen for drugs which might be expected to interfere with ionic events and thereby to interfere with self proliferation. The hypothesis is that drugs which interfere with stimulation of self proliferation in one cell system would be expected to interfere with stimulation of cell proliferation in other cell systems. Amiloride [2609-46-3] and seven of its analogs, as well as seven substances of other structural types, all of which control electrolyte transport, were tested for their effectiveness for inhibiting the progesterone-stimulated meiotic maturation cycle of oocytes from the amphibian Xenopus laevis. Data were also collected on the ability of all oocytes to recover from the drug's inhibitory effect and on the toxicity of each drug. The data revealed that up to a 14-fold difference exists in the 50% inhibitory concentration between substances, the recovery from the drug's

inhibitor effect range from non-reversible to almost complete reversibility, and that toxicity, as measured by failure to exclude trypan blue, ranged from 0-57%. In some, but not all cases, the failure to recover from the drug's inhibitory effects could be correlated to the drug's toxic effects. Amiloride which has been shown to be a reversible inhibitor of cell proliferation in rapidly dividing mammalian cell populations has similar properties on the oocyte maturation division cycle of X. laevis.

IT 90689-42-2
RL: BIOL (Biological study)
(meiosis inhibition by, cytotoxic agent screening in oocytes in relation to)

RN 90689-42-2 CAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



L6 ANSWER 107 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1984:17226 CAPLUS

DOCUMENT NUMBER: 100:17226

TITLE: Inhibition of sodium-dependent calcium efflux from heart mitochondria by amiloride analogs

AUTHOR(S): Jurkowitz, Marianne S.; Altschuld, Ruth A.; Brierley, Gerald P.; Cragoe, Edward J., Jr.

CORPORATE SOURCE: Dep. Physiol. Chem., Ohio State Univ., Columbus, OH, 43210, USA

SOURCE: FEBS Letters (1983), 162(2), 262-5
CODEN: FEBLAL; ISSN: 0014-5793

DOCUMENT TYPE: Journal

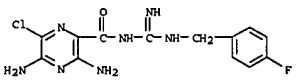
LANGUAGE: English

AB The Na+-induced release of accumulated Ca2+ from heart mitochondria was inhibited by amiloride [2609-46-3], benzamil [2898-76-2], and several other amiloride analogs. These drugs did not affect uptake or release of Ca2+ mediated by the ruthenium red-sensitive uniporter and their effects, like those of diltiazem and other Ca2+-antagonists, appear to be localized principally at the Na+/Ca2+ antiporter of the mitochondrion. Benzamil inhibits Na+/Ca2+ antiport non-competitively with respect to [Na+] with a Ki of 167 μM. In the presence of 1.5 mM, Pi the Ki for benzamil inhibition of this reaction is decreased to 87 μM. Structure-activity relations for the effect of amiloride analogs on Na+-dependent Ca2+ efflux are given.

IT 1634-16-8
RL: BIOL (Biological study)
(sodium-dependent calcium efflux from heart mitochondria response to)

RN 1634-16-8 CAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(4-fluorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



L6 ANSWER 108 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1983:537522 CAPLUS

DOCUMENT NUMBER: 99:137522

TITLE: Inhibition of sodium influx and DNA synthesis in human fibroblasts and neuroblastoma-glioma hybrid cells by amiloride analogs

AUTHOR(S): O'Donnell, Martha E.; Cragoe, Edward, Jr.; Villereal, Mitchel L.

CORPORATE SOURCE: Dep. Pharmacol. Physiol. Sci., Univ. Chicago, Chicago, IL, 60367, USA

SOURCE: Journal of Pharmacology and Experimental Therapeutics (1983), 226(2), 368-72
CODEN: JPETAB; ISSN: 0022-3565

DOCUMENT TYPE: Journal

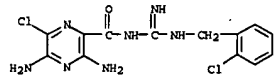
LANGUAGE: English

AB A number of amiloride analogs were examined for potency of Na+ influx inhibition in human fibroblasts (HSWP). One analog, benzamil, exhibited a 60-fold enhanced potency relative to amiloride. The relative efficacies with which amiloride and benzamil inhibit Na+ influx and DNA synthesis in HSWP cells and neuroblastoma-glioma hybrid cells (NG108-15) were also assessed. Concns. of benzamil required for 50% inhibition (ID50) of Na+ influx and DNA synthesis of HSWP cells are in excellent agreement (15 and 18 μM, resp.), an observation which, on the surface, is supportive of the hypothesis in question. Benzamil also inhibits Na+ influx of NG108-15 cells with an ID50 comparable to that for HSWP cells (18 μM) and suppresses DNA synthesis with a slightly higher ID50 (38 μM). Although the benzamil concns. needed to inhibit cell growth and Na+ influx are in reasonable agreement, caution should be exercised in interpreting the effects of benzamil on cell growth with respect to the role of Na+ influx, as it was also observed that an analog of benzamil with a reduced ability to inhibit Na+ influx gave inhibition of DNA synthesis at concns. which do not inhibit Na+ influx.

IT 1163-44-6 1163-45-7
RL: BIOL (Biological study)
(4NA formation and sodium transports by salts of human and laboratory animal inhibition by)

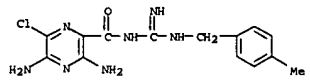
RN 1163-44-6 CAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2-chlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



RN 1163-45-7 CAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[(4-methylphenyl)methyl]amino]methyl]-(9CI) (CA INDEX NAME)



L6 ANSWER 109 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1978:557177 CAPLUS

DOCUMENT NUMBER: 89:157177

TITLE: Effects of some pyrazinecarboxamides on sodium transport in frog skin

AUTHOR(S): Cuthbert, A. W.; Fanelli, G. M.

CORPORATE SOURCE: Dep. Pharmacol., Univ. Cambridge, Cambridge, UK

SOURCE: British Journal of Pharmacology (1978), 63(1), 139-49
CODEN: BJPCBM; ISSN: 0007-1188

DOCUMENT TYPE: Journal

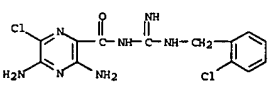
LANGUAGE: English

AB The dissociation constant of amiloride (I) [2609-46-3] for passive Na channels in isolated frog (Rana temporaria) skin was 181.9 nM and the maximum percentage inhibition was 101.3% when measured at a Na concentration of 111 mM; the N-benzylamidino and N-o-chlorobenzylamidino analogs had affinities .apprx.20 times greater than those of I and produced maximum inhibition of transport. Substitution of Br for Cl in position 6 had no effect on I activity, whereas the iodo derivative had 15% of the affinity of I. Substitution in the 5-amino group in 10 compds. reduced the affinities to <1% of that of I, without affecting their ability to completely inhibit transport. N-amidino-3,5-diaminopyrazinecarboxamide [1134-13-0] was unique in showing a nonlinear concentration-response curve.

IT 1163-44-6
RL: BIOL (Biological study)
(sodium transport by skin inhibition by)

RN 1163-44-6 CAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2-chlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



L6 ANSWER 110 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1978:509585 CAPLUS

DOCUMENT NUMBER: 89:109585

TITLE: Pyrazinecarboxamides

INVENTOR(S): Cragoe, Edward J., Jr.; Woltersdorf, Otto W., Jr.; Habecker, Charles N.

PATENT ASSIGNEE(S): Merck and Co., Inc., USA

SOURCE: U.S., 15 pp.
CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

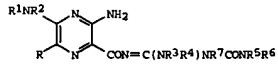
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 4085211	A	19780418	US 1976-722442	19760913
DK 7605314	A	19770616	DK 1976-5314	19761125
SE 7613289	A	19770616	SE 1976-13289	19761126
SE 431452	B	19840206		
SE 431452	C	19840517		
NL 7613276	A	19770617	NL 1976-13276	19761129
AU 7620181	A	19780608	AU 1976-20181	19761202
AU 511429	B2	19800821		
ES 454160	A1	19780301	ES 1976-454160	19761210
FR 2335226	A1	19770715	FR 1976-37459	19761213
FR 2335226	B1	19790309		
GB 1527297	A	19781004	GB 1976-51940	19761213
HU 175504	B	19800828	HU 1976-ME2034	19761213
CH 630369	A5	19820615	CH 1976-15660	19761213
BE 849379	A1	19770614	BE 1976-173235	19761214
ZA 7607431	A	19780726	ZA 1976-7431	19761214
JP 52106877	A	19770907	JP 1976-149889	19761215
JP 62038350	B	19870817		
ES 465742	A1	19781001	ES 1978-465742	19780103

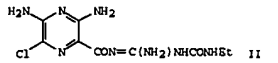
PRIORITY APPLN. INFO.: US 1975-640803 A2 19751215

OTHER SOURCE(S): MARPAT 89:109585

GI



I



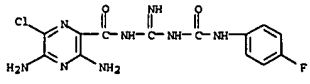
II

AB A series of title amides I (R = halo; R1 = H, alkyl, cycloalkyl, alkenyl; R2 = H, alkyl; NR1R2 = pyrrolidino, piperidino; R3 = H, alkyl, cycloalkyl; R4 = H, alkyl, cycloalkyl; R5 = H, alkyl, cycloalkyl, Ph, substituted phenyl; R6 = H, alkyl, cycloalkyl; NR5R6 = morpholino, piperazino; R7 = H, alkyl; R3R7 = CH2CH2, substituted ethylene) were prepared and are useful as diuretics (no data). Thus, the addition reaction of N-amidino-3,5-diamino-6-chloro-2-pyrazinecarboxamidewith EtNCO gave II.

IT 64077-55-0P 64077-56-1P 67376-91-4P
67376-92-5P 67376-93-6P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

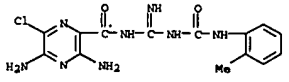
RN 64077-55-0 CAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[[(4-fluorophenyl)amino]carbonyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)

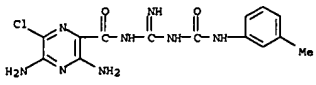


RN 64077-56-1 CAPLUS

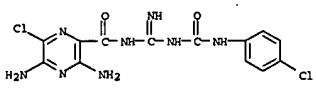
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[[(2-methylphenyl)amino]carbonyl]amino]methyl]-(9CI) (CA INDEX NAME)



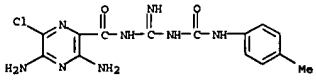
RN 67376-91-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[[(3-methylphenyl)amino]carbonyl]amino]methyl]-(9CI) (CA INDEX NAME)



RN 67376-92-5 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[[(4-chlorophenyl)amino]carbonyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



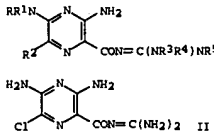
RN 67376-93-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[[(4-methylphenyl)amino]carbonyl]amino]methyl]-(9CI) (CA INDEX NAME)



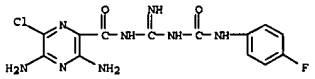
L6 ANSWER 111 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1977:517906 CAPLUS
DOCUMENT NUMBER: 87:117906
TITLE: Pyrazinecarboxamides
INVENTOR(S): Cragoe, Edward Jethro, Jr.; Woltersdorf, Otto William, Jr.; Habecker, Charles Newcomer
PATENT ASSIGNEE(S): Merck and Co., Inc., USA
SOURCE: Ger. Offen., 71 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 2656374	A1	19770616	DE 1976-2656374	19761213
DE 2656374	C2	19890810		
DK 7605314	A	19770616	DK 1976-5314	19761125
SE 7613289	A	19770616	SE 1976-13289	19761126
SE 431452	B	19840206		
SE 431452	C	19840517		
NL 7613276	A	19770617	NL 1976-13276	19761129
AU 7620181	A	19780608	AU 1976-20181	19761202
AU 511429	B2	19800821		
ES 454160	A1	19780301	ES 1976-454160	19761210
FR 2335226	A1	19770715	FR 1976-37459	19761213
FR 2335226	B1	19790309		
GB 1527297	A	19781004	GB 1976-51940	19761213
HU 175504	B	19800828	HU 1976-ME2034	19761213
CH 630369	A5	19820615	CH 1976-15660	19761213
BE 849379	A1	19770614	BE 1976-173235	19761214
ZA 7607431	A	19780726	ZA 1976-7431	19761214
JP 52106877	A	19770907	JP 1976-149889	19761215
JP 62038350	B	19870817		
ES 465742	A1	19781001	ES 1978-465742	19780103

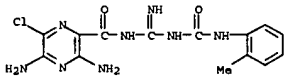
PRIORITY APPLN. INFO.: US 1975-640803 A 19751215
GI



AB Diuretic (no data) pyrazinecarboxamides I (R, R1, R3, R4, R5, R7 = H, alkyl; R2 = halo; R6 = H, alkyl, aryl) (>60 compds.) were prepared Thus II was treated with PrNCO to give I (R, R1, R3, R4, R5, R7 = H, R2 = Cl, R6 = Pr).
IT 64077-55-0P 64077-56-1P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
RN 64077-55-0 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[[(4-fluorophenyl)amino]carbonyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



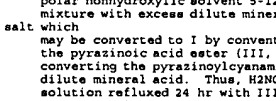
RN 64077-56-1 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[[(2-methylphenyl)amino]carbonyl]amino]methyl]-(9CI) (CA INDEX NAME)



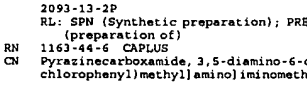
L6 ANSWER 112 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1971:42387 CAPLUS
DOCUMENT NUMBER: 74:42387
TITLE: Diuretic and natriuretic pyrazinoylguanidines from pyrazinoylureas
INVENTOR(S): Tull, Roger J.; Pollak, Peter I.
PATENT ASSIGNEE(S): Merck and Co., Inc.
SOURCE: U.S., 4 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 3539569	A	19701110	US 1968-754451	19680821
NL 6910945	A	19700224	NL 1969-10945	19690716

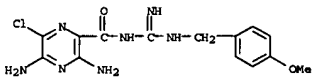
PRIORITY APPLN. INFO.: US 1968-754451 A 19680821
GI For diagram(s), see printed CA Issue.
AB The title process describes the preparation of pyrazinoylguanidines (I) by treatment of the corresponding pyrazinoylureas (II) with a guanidine in a polar nonhydroxylic solvent 5-12 hr at 50-100°, treatment of the mixture with excess dilute mineral acid to precipitate I as the acid addition salt which may be converted to I by conventional procedures. II are obtained from the pyrazinoic acid ester (III, X = OR') by refluxing with NaHNCN and converting the pyrazinoylcyanamide III (X = NHCN) to II by treatment with dilute mineral acid. Thus, H2NCN in MeOH containing Na refluxed 30 min and the solution refluxed 24 hr with III (R1 = R2 = H, X = OMe) gave III (R1 = R2 = H, X = NHCN) (IV), m. >330°. V in DMF stirred (N atmospheric) 8 hr at 70° with H2NC(:NH)NH2.HCl and NaOMe and treated at 40° with 1.5N HCl gave I (R1 = R2 = H, X = Cl), m. 240.5-1.5°. An addnl. 30 compds. obtained by slight modifications of the process are reported.
IT 1163-44-6P 1163-45-7P 1165-90-8P
2093-13-2P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
RN 1163-44-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2-chlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



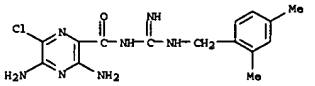
RN 1163-45-7 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[(4-methylphenyl)methyl]amino]methyl]-(9CI) (CA INDEX NAME)



RN 1165-90-8 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[(4-methoxyphenyl)methyl]amino]methyl]-(9CI) (CA INDEX NAME)



RN 2093-13-2 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2,4-dimethylphenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



L6 ANSWER 113 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1970:43731 CAPLUS
DOCUMENT NUMBER: 72:43731
TITLE: Diuretic and natriuretic pyrazinoylguanidines
INVENTOR(S): Cragoe, Edward J., Jr.; Jones, James Holden
PATENT ASSIGNEE(S): Merck and Co., Inc.
SOURCE: Fr., 22 pp.
CODEN: FRXXAK
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

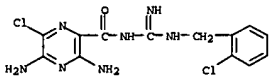
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
FR 1559541		19690307	FR	19680412
DE 1770174			DE	
GB 1185408			GB	
US 3527758		19700908	US	19670413
ZA 6802332		19680000	ZA	

PRIORITY APPLN. INFO.: US 19670413
AB Pyrazinoylguanidines, useful as diuretic and natriuretic agents for reducing the excretion of K ions are prepared by treating a pyrazinoic acid azide with a guanidine. Thus, to a solution of 10 g methyl 3-amino-5-diethylamino-6-chloropyrazinoate in 250 ml EtOH, 20 ml 64% aqueous N2H3 is added and the mixture refluxed 4 hr to give 9 g (87%) 3-amino-5-diethylamino-6-chloropyrazinoicacid hydrazide m. 142-5° (2-propanol). The following I were prepared (R, R1, and m.p. given): EtNH, Cl, 168-70°; CH2:CHCH2NH, Cl, 158-60°; Me2N, Me, -; EtNMe, Cl, 134-6°; Me2N, Cl, 132-4°; p-ClC6H4CH2NH, Cl, 158-60°; Ph, Me, -; MeNH, Cl, 257-60°; BuNH, Cl, 162-5°; PrNH, Cl, 171-3°; HOCH2CH2NH, Cl, 184-5°; C6H13, Cl, -; cyclopentylamino, Cl, 143-5°; Me2NCH2CH2NH, Cl, 161-3°; MeS, Cl, 240-2°; HS, Cl, 218-20°; cyclopropyl-methylamino, Cl, -; HO, Cl, >30°; PrS, Cl, 166-8°; Me, Br, 202-5°; cyclopropylamino, Cl, -; p-MeC6H4CH2NH, Cl, -; p-ClC6H4NH, Cl, -; PhCH2CH2NH, Cl, -; Me2N, Ph, 153-4°; CF3CH2NH, Cl, -; 4-pyridylmethylamino, Cl, -; furfurylamino, Cl, -; EtS, Cl, 196-9°; n-C5H11S, Cl, 265-7° (HCl); Me(CH2CH:CH2)N, Cl, -; pyrrolidino, Cl, -; MeN-Pr, Cl, 133-6°; PhCH2S, Cl, -; H, Br, -. A solution of 3.45 g NaNO2 in 20 ml

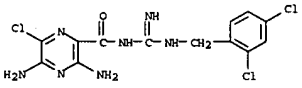
H2O was added to a solution of 10 g 3,5 -diamino-6-chloropyrazinoicacid hydrazide in 350 ml 0.5N HCl at 50-5° during 45 min to give 6.4 g 3,5-diamino-6-chloropyrazinoicacid azide (II), m. 160° (explodes). To a solution of 0.46 g Na in 50 ml 2-propanol, 2 g guanidine-HCl was added, the mixture cooled, NaCl separated by filtration, 1.07 g II added to the filtrate the mixture refluxed 30 min., worked up and treated with HCl to give 0.4 g (3,5-diamino-6-chloropyrazinoyl)guanidine-HCl.2H2O,m. 285-8°; free base m. 240.5-1.5°. The following III (R2 = R3 = R4 = H) were prepared (R, R1 and m.p. given): Et2N, Cl, 215°; EtNH, Cl, 217-18°; CH2CHCH2NH, Cl, 213-14°; Me2N, Me, 262°; MeNEt, Cl, 229-30°; iso-PrNH, Cl, 215°; p-ClC6H4-CH2NH, Cl, 225-6°; Ph, Me, -; MeNH, Cl, 238-9°; BuNH, Cl, 219.5°; PrNH, Cl, 221-2°; HO(CH2)2NH, Cl, 272-3°; n-C6H13, Cl, -; cyclopentylamino, Cl, 219-20°; Me2N(CH2)2NH, Cl, 192.5-4.5°; MeS, Cl, 234.5-6.5°; HS, Cl, 236.5°; cyclo-propylmethylamino, Cl, 220.0-1.5°; HO, Cl, <310°; PrS, Cl, -; Me, Br, 288°; cyclopropylmethylamino, Cl, 213-15°; p-MeC6H4CH2NH, Cl, 216-17°; p-ClC6H4NH, Cl, 276-8°; Ph-(CH2)2NH, Cl 199-202°; Me2N, Ph, 205-6°; CP3CH2NH, Cl, 232-3°; 4-pyridylmethylamino, Cl, 239-40°; furfurylamino, Cl, 217-18°; EtS, Cl, -; n-C5H11S, Cl, -; Me(CH2CH:CH2)-N, Cl, 207-8°; pyrrolidino, Cl, 244.5-5.5°; MeNPr, Cl, 214-15°; Me2N, Cl, 216-17°. The following III (R1 = Cl, R2 = H) were prepared (R, R3, R4, and m.p. given): NH2, H, HOCH2CH2, 228.5-9.5°; NH2, H, Ph, 272°; NH2, H, PhCH2, 215-16°; NH2, H, p-FC6H4CH2, 216.0-19.5°; NH2, H, PhCH(Me), 153-60°; NH2, H, 2-methylnaphthyl, 243.5-5.5°; NH2, H, 3-pyridylmethyl, 280.5-3.5°; NH2, H, p-MeC6H4CH2, 210-12°; NH2, Me, PhCH2, 274.5°; NH2, H, o-ClC6H4CH2, 220-3°; NH2, H, p-ClC6H4CH2, 204-6°; NH2, H, p-MeOCH4CH2, 175.5-9.6°; NH2, H, 1,3-Me2C6H3CH2, 267.5-70.5°; NH2, H, 3,4-Cl2C6H3-CH2, 216-19°; NH2, H, Ph(CH2)2, 219.0-21.5°; NH2, Me, Me, 275°; NH2, Et, Et, 265°; NH2, Bu, Bu, 148-9°; NH2 (R3R4 =) (CH2)4, -; NH2, (R3R4 =) (CH2)2O(CH2)3, -; Me2CHNH2, Me, Me, 238.5-40.5°; CH2:CHCH2, Me, Me, 213-15°; BuNH, Me, Me, 187.5°; cyclopropylmethylamino, Me, Me, 196-7°; Me2N, Me, Me, 219°; MeNEt, Me, Me, 217-18°; Et2N, Me, Me, 212-14°. Also prepared was III (R = R2 = R3 = R4 = H, R1 = Br) and III (R = NH2, R1 = Cl, R2 = R3 = Me, and R4 = H).

IT 1163-44-6P 1163-45-7P 1165-90-8P
1166-01-4P 1634-16-8P 1636-56-2P
2088-58-6P 2093-13-2P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

RN 1163-44-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2-chlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)

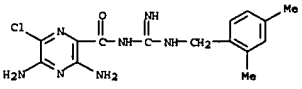


RN 1163-45-7 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[(4-methylphenyl)methyl]amino]methyl]-(9CI) (CA INDEX NAME)



● HCl

RN 2093-13-2 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2,4-dimethylphenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)

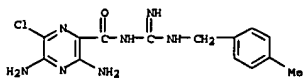


L6 ANSWER 114 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1969:512983 CAPLUS
DOCUMENT NUMBER: 71:112983
TITLE: (3,5-Diamino-6-halopyrazinoyl)guanidines
INVENTOR(S): Pollak, Peter I.; Tull, Roger J.
PATENT ASSIGNEE(S): Merck and Co., Inc.
SOURCE: Fr., 8 pp.
CODEN: FRXXAK
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

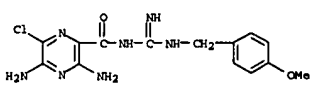
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
FR 1525692		19680517	FR 1967-109143	19670605
GB 1180785			GB	
US 3472847		19691014	US	19660825
ZA 6703250		19670000	ZA	
PRIORITY APPLN. INFO.:			US	19660825

GI For diagram(s), see printed CA Issue.

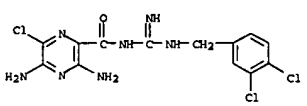
AB The title compds. (I) are prepared by reacting a 3,5-diamino-6-halopyrazinoylcyanamide (II) with NH3 or an amine and are useful as diuretics. Thus, 1 mole methyl 6-chloro-3,5-diaminopyrazinecarboxylatein MeOH is treated with 1 mole sodium cyanamide and refluxed 3 hrs., the solvent evaporated and the residue dissolved in 1 l. concentrated NH4OH containing 3 moles NH4Cl and heated 3 hrs. (pH = 8), to yield I (R1 = R2 = R3 = R4 = H, R = Cl), m. 240.5-1.56° (decomposition); HCl salt m. 293.5°. Similarly was prepared the following I (R = Cl, R1 = R2 = R4 = H) (R3 and m.p. given): Me, 252-4°; CH2CH2OH, - (HCl salt m. 228.5-9.5°); benzyl, 215-16°; o-ClC6H4CH2, 220-3°; p-FC6H4CH2, 216-19.5°; p-MeC6H4CH2, 210-12°; p-MeOC6H4CH2, 175.5-9.5°; 2,4-Me2C6H3CH2, 220-2°; Ph-CHMe, 152-60°; PhCH2CH2, 219-21.5; 3-pyridylmethyl, - (2HCl salt m. 280.5-3.5°.



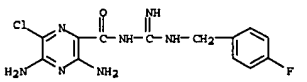
RN 1165-90-8 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[(4-methoxyphenyl)methyl]amino]methyl]-(9CI) (CA INDEX NAME)



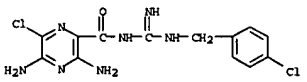
RN 1166-01-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(3,4-dichlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



RN 1634-16-8 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(4-fluorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



RN 1636-56-2 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[(p-chlorobenzyl)amidino]-(7CI, 8CI) (CA INDEX NAME)

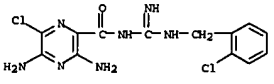


RN 2088-58-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2,4-dichlorophenyl)methyl]amino]iminomethyl]-,monohydrochloride (9CI) (CA

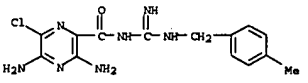
Also the following I (R = Cl, R1 = Me, R3 = R4 = H) (R2 and m.p. given); Me, 216-17°; Et, 229-30°; Pr, 214-15°; iso-Pr, 207-8°. Also I (R = Cl, R1 = H, R3 = R4 = Me (same data given): H, - (HCl.H2O m. 277°); iso-Pr, 238.5-40°; allyl, 213-15°; Bu, 187-5°. Also I (R = Cl, R1 = R4 = H) (R2, R3, and m.p. given): iso-Pr, Me, 300°; iso-Pr, CH2CH2OH, - (HCl semihydrate 185-6°); iso-Pr, PhCH2, 200.5-4.5°; allyl, H, 213-14°; cyclopropylmethyl, H, 220-1.5°. Also the following I (R, R1, R2, R3, R4, and m.p. given); Cl, iso-Pr, H, Me, Me, 238.5-40°; Br, H, H, H, H, 232.5-5.5°; Cl, H, H, Et, Et, 265°; Cl, H, H, Me, PhCH2, - (HCl salt m. 274.5°); Cl, Me, iso-Pr, Me, Me, 209-11°; Cl, Et, Et, Me, Me, 212-14°.

IT 1163-44-6P 1163-45-7P 1165-90-8P
1634-16-8P 2093-13-2P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

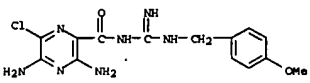
RN 1163-44-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2-chlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



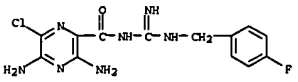
RN 1163-45-7 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[(4-methylphenyl)methyl]amino]methyl]-(9CI) (CA INDEX NAME)



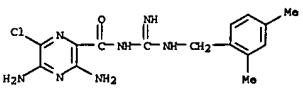
RN 1165-90-8 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[(4-methoxyphenyl)methyl]amino]methyl]-(9CI) (CA INDEX NAME)



RN 1634-16-8 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(4-fluorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



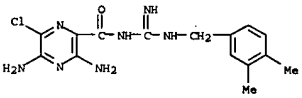
RN 2093-13-2 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2,4-dimethylphenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



L6 ANSWER 115 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1969:491530 CAPLUS
DOCUMENT NUMBER: 71:91530
TITLE: (3,5-Diamino-6-halopyrazinoyl)guanidines
INVENTOR(S): Pollak, Peter I.; Tull, Roger J.
PATENT ASSIGNEE(S): Merck and Co., Inc.
SOURCE: Fr., 9 pp.
CODEN: FRXXAK
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
FR 1528217		19680607	FR 1967-109146	19670605
GB 1173451			GB	
US 3503972		19700331	US	19681104
ZA 6703247		19670000	ZA	
PRIORITY APPLN. INFO.:			US	19660825

GI For diagram(s), see printed CA Issue.
AB I compds. are prepared Thus, Me 3,5-diamino-6-chloropyrazinoateis converted to 3,5-diamino-6-chloropyrazinamidewhich is dehydrated to II (R = CN) (III), m. 295°. III (1 mole) is treated with 1.1 moles EtOH and 1.1 moles HCl at 0° to give II [R = C(OEt):NH]-HCl which is heated with EtOH to give II [R = C(OEt)3] (IV). A mixture of 1 mole IV, 1 mole guanidine, and 2 moles Ac2O is heated 1 hr. at 140° to give II [R = C(OEt):NC(:NH)NH2] which is heated 5 hrs. with 2N HCl to give (3,5-diamino-6-chloropyrazinoyl)guanidine-HCl,m. 293.5° (decomposition) Similarly prepared are the following I (n = 0, R4 = H) [R, R1, R2, R3, and m.p. (decomposition) given]: H, H, Me, H 252-4°; H, H, Me, Me, - (HCl salt monohydrate m. 277°); H, H, Et, Et, 265°; H, H, Me, PhCH2, - (HCl salt m. 274.5°); H, H, CH2CH2OH, H, - (HCl salt m. 228.5-9.5°); H, H, PhCH2, H, 215-16°; H, H, m-ClC6H4CH2, H, 220-3°; H, H, p-FC6H4CH2, H, 216-19.5°; H, H, p-MeC6H4CH2, H, 210-12°; H, H, p-MeOC6H4CH2, H, 175.5-9.5°; H, H, 3,4-Me2C6H3CH2, H, 220-2°; H, H, PhCHMe, H, 152-60°; H, H, PhCH2CH2, H, 219-21.5°; H, H, 3-pyridylmethyl, H, - (2HCl salt m. 280.5-3.5°); H, iso-Pr, Me, H, >300°; H, iso-Pr, Me, Me, 238.5-40°; H, iso-Pr, CH2CH2OH, H, - (HCl salt hemihydrate m. 185-6°); H, iso-Pr, PhCH2, H, 200.5-4.5°; H, allyl, H, H, 213-14°; H, allyl, Me, Me, 213-15°; H, Bu, Me, Me, 187.5°; H, cyclopropyl, H, H, 220-1.5°; Me, Me, H, H, 216-17°; Me, Et, H, H, 229-30°; Me, Pr, H, H, 214-15°; Me, iso-Pr, H, H, 207-8°; Me, iso-Pr, Me, Me, 209-11°; Et, Et, Me, Me, 212-14°; (3,5-diamino-6-pyrazinamido)guanidine-HCl, m. 281-2° (decomposition); I (n = 1, R = R1 = Me, R2 = R3 = R4 = H), m. 221° (decomposition); I (n = 1, R = R1 = R4 = H, R2 = R3 = Me)-HCl, m. 279-80° (decomposition); (3,5-diamino-6-bromopyrazinoyl)guanidine, m. 232.5-5.5°; I [n = 0, R = R1 = R2 = H, (R3R4 =) CH2CH2], m. 222.5-3.5°.
IT 1163-45-7P 1165-90-8P 1634-16-8P 23697-97-4P 23765-86-8P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

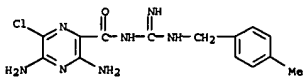


RN 23765-86-8 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[(3,4-dimethylbenzyl)amidino]-(8CI) (CA INDEX NAME)

L6 ANSWER 116 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1969:481411 CAPLUS
DOCUMENT NUMBER: 71:81411
TITLE: (3,5-Diamino-6-halopyrazinoyland - pyrazinamido)guanidines
INVENTOR(S): Pollak, Peter I.; Tull, Roger J.
PATENT ASSIGNEE(S): Merck and Co., Inc.
SOURCE: Fr., 6 pp.
CODEN: FRXXAK
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

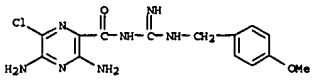
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
FR 1525671		19680517	FR 1967-109099	19670605
GB 1158399			GB	
ZA 6703261		19670000	ZA	
PRIORITY APPLN. INFO.:			US	19660825

GI For diagram(s), see printed CA Issue.
AB Pyrazinoic acids are treated with guanidines h2N(NH)nC(:NR)NR1R2 to give compds. I. A mixture of 1 mole 6-chloro-3,5-diaminopyrazinoicacid, 3 moles guanidine, and 500 ml. BuOH is refluxed 8 hrs. to give (3,5-diamino-6-chloropyrazinoyl)guanidine,m. 240-1.50° (decomposition). Similarly prepared are the following I (X = Cl, n = O, R = H) (R1, R2, R3, R4, and decomposition temperature given): Me, H, H, H, 252-4°; Me, Me, H, H, -, HCl salt monohydrate decompose 277°; Et, Et, H, H, 265°; Me, PhCH2, H, H, -, HCl salt decompose 274.5°; CH2CH2OH, H, H, H, HCl salt m. 228.5-9.5°; PhCH2, H, H, H, 215-16°; o-ClC6H4CH2, H, H, H, 220-3°; p-FC6H4CH2, H, H, H, 216-19.5; p-MeC6H4CH2, H, H, H, 210-12°; p-MeOC6H4CH2, H, H, H, 175.5-9.5°; 2,4-Me2C6H3CH2, H, H, H, 220-2°; PhCHMe, H, H, H, 152-60°; PhCH2CH2, H, H, H, 219-21.5°; 3-pyridylmethyl, H, H, H, -, 2HCl salt decompose 280-3.5°; Me, H, H, iso-Pr, >300°; Me, Me, H, iso-Pr, 238.5-40°; CH2CH2OH, H, H, iso-Pr, -, HCl salt hemihydrate decompose 185-6°; PhCH2, H, H, iso-Pr, 200.5-4.5; H, H, H, allyl, 213-14°; Me, Me, H, allyl, 213-15°; Me, Me, H, Bu, 187.5°; H, H, H, cyclopropylmethyl, 220-1.5°; H, H, Me, Me, 216-17°; H, H, Me, Et, 229-30°; H, H, Me, Pr [sic], 214-15°; H, H, Me, iso-Pr, 207-8°; Me, Me, Me, iso-Pr, 209-11°; Me, Me, Et, Et, 212-14°; and the following compds. (decomposition temperature given): I (X = Cl, n = 1, R = R1 = R2 = R3 = R4 = H)-HCl, 281-2°; I (X = Cl, n = 1, R = R1 = R2 = H, R3 = R4 = Me), 221°; I (X = Cl, n = 1, R = R3 = R4 = H, R1 = R2 = Me)-HCl, 279-80°; I (X = Br, n = 0, R = R1 = R2 = R3 = R4 = H), 232.5-5.5°; I [X = Cl, n = O, (RR2N =) ethyleneimino, R1 = R3 = R4 = H] (sic), 222.5-3.5°.
IT 1163-44-6P 1163-45-7P 1165-90-8P

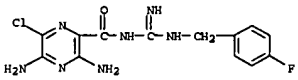


RN 1163-45-7 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[(4-methylphenyl)methyl]amino]methyl]-(9CI) (CA INDEX NAME)

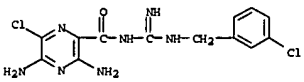
RN 1165-90-8 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[(4-methoxyphenyl)methyl]amino]methyl]-(9CI) (CA INDEX NAME)



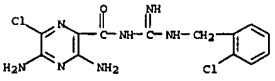
RN 1634-16-8 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(4-fluorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



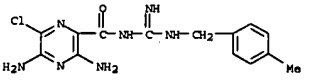
RN 23697-97-4 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[(m-chlorobenzyl)amidino]-(8CI) (CA INDEX NAME)



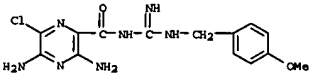
1634-16-8P 2093-13-2P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
RN 1163-44-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2-chlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



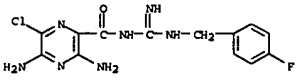
RN 1163-45-7 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[(4-methylphenyl)methyl]amino]methyl]-(9CI) (CA INDEX NAME)



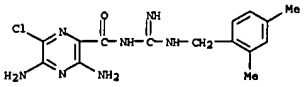
RN 1165-90-8 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[(4-methoxyphenyl)methyl]amino]methyl]-(9CI) (CA INDEX NAME)



RN 1634-16-8 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(4-fluorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



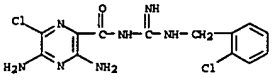
RN 2093-13-2 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2,4-dimethylphenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



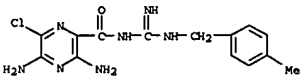
L6 ANSWER 117 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1969:439006 CAPLUS
DOCUMENT NUMBER: 71:39006
TITLE: 1-(2-Pyrazinylcarbonyl)guanidines
INVENTOR(S): Pollak, Peter I.; Tull, Roger J.
PATENT ASSIGNEE(S): Merck and Co., Inc.
SOURCE: Brit., 6 pp.
CODEN: BRXXAA
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
GB 1145934		19690319	GB 1967-26217	19670607
DE 1695421			DE	
FR 1525670			FR	
ZA 6703251		19670000	ZA	

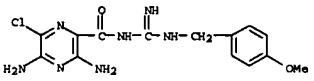
PRIORITY APPLN. INFO.: US 19660825
GI For diagram(s), see printed CA Issue.
AB The title compds. I are prepared by chlorination of the corresponding 1-[3,5-diamino-2-pyrazinylcarbonyl(orpyrazinylcarbonylamino)]guanidinein aqueous AcOH. Thus, 0.6 mole NH2C(:NH)NH2.HCl was added to a stirred solution of 0.6 mole Na in 2 l. absolute EtOH under N, the mixture filtered, 0.6 mole Me 3,5-diamino-2-pyrazinecarboxylateadded to the filtrate, and the mixture heated to 60° to give 1-(3,5-diamino-2-pyrazinylcarbonyl)guanidine (II), m. 286-8° (decomposition). A mixture of 0.6 mole II, 750 ml. AcOH, and 3 l.H2O was heated to 40° and 140 g. Cl passed into the solution during 30 min. to yield 1-(3,5-diamino-6-chloro-2-pyrazinylcarbonyl)guanidine,m. 240.5-1.5° (decomposition). Likewise prepared are I (R1, R2, n, R3, R4, and m.p. (decomposition given): Me, Me, 0, H, H, 216-17° (prepared from 1-[3-amino-5-(dimethylamino-2-pyrazinylcarbonyl)guanidinem. 224-5°); PhCH2, H, 0, H, H -(prepared from 1-[3-amino-5-benzylamino-2-pyrazinylcarbonyl]-guanidinem. 231-3°); H, H, 1, H, H, - (HCl salt m. 281-2°); Me, Me, 1, H, H, 221°; H, H, 0, Me, H, 252-4°; H, H, 0, Me, Me, 295°; H, H, 0, Et, Et, 265°; H, H, 0, Me, PhCH2, - (HCl salt m. 274.5°); H, H, 0, HOCH2CH2,H, - (HCL salt m. 228.5-9.5°); H, H, 0, PhCH2, H, 215-16° (2HCl salt m. 280-3.5°); H, H, 0, o-ClC6H4CH2, H, 220-3°; H, H, 0, pFC6H4CH2, H, 216-19.5°; H, H, 0, p-MeC6H4CH2, H, 210-12°; H, H, 0, p-Me-OC6H4CH2, H, 175.5-9.5°; H, H, 0, 2,4-Me2C6H4CH2, H, 220-2°; H, H, 0, PhCHMe, H, 152-60°; H, H, 0, PhCH2CH2, H, 219-21.5°; H, H, 1, Me, Me, 279-80°; also prepared was 2-(3,5-diamino-6-chloro-2-pyrazinylcarbonylamino)-2-imidazoline m. 222.5-3.5°. I are useful as diuretics and selectively enhance Na and Cl ion excretion while suppressing K ion excretion.
IT 1163-44-6P 1163-45-7P 1165-90-8P
1634-16-8P 2093-13-2P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
RN 1163-44-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2-chlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



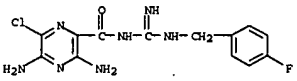
RN 1163-45-7 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[(4-methylphenyl)methyl]amino]methyl]-(9CI) (CA INDEX NAME)



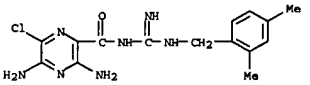
RN 1165-90-8 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[(4-methoxyphenyl)methyl]amino]methyl]-(9CI) (CA INDEX NAME)



RN 1634-16-8 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(4-fluorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



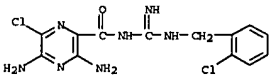
RN 2093-13-2 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2,4-dimethylphenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



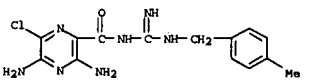
L6 ANSWER 118 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1969:96820 CAPLUS
DOCUMENT NUMBER: 70:96820
TITLE: Pyrazinoylguanidine and pyrazinamidoguanidine
INVENTOR(S): Pollak, Peter I.; Tull, Roger J.
PATENT ASSIGNEE(S): Merck and Co., Inc.
SOURCE: U.S., 4 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 3432502	A	19690311	US 1966-574909	19660825
NL 6707563	A	19680226	NL 1967-7563	19670531
DK 115771	B	19691110	DK 1967-2864	19670601
BE 699435	A	19671204	BE 1967-699435	19670602
ES 341321	A1	19681016	ES 1967-341321	19670602
CH 484161	A	19700115	CH 1967-484161	19670607
GB 1184709	A	19700318	GB 1967-1184709	19670607

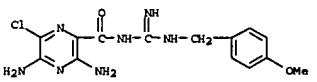
PRIORITY APPLN. INFO.: US 1966-574909 A 19660825
GI For diagram(s), see printed CA Issue.
AB (3,5-Diamino-6-halopyrazinoyl)guanidineand (3,5-diamino-6-halopyrazinamido)guanidine, possessing diuretic and saluretic properties without enhancing K excretion, are prepared by treating 3,5-diamino-6-halopyrazinoic acid hydrazide with a guanidine or an aminoguanidine. Thus, 1 mole 6-choro-3,5-diaminopyrazinoicacid hydrazide and 3 moles chloral were heated 2 hrs. at 80° in 300 ml. dimethoxyethane. The solution was then cooled to room temperature and 1 mole guanidine added with stirring. The mixture was heated an addnl. 2 hrs. at 80° removing most of the solvent by distillation and the product (6-chloro-3,5-diaminopyrazinoyl)guanidinewas precipitated by addition of 300 ml. N HCl yielding the HCl salt, m. 293.5° (decompose). Similarly prepared were I (n, R, R1, R2, R3, R4, R5, and m.p. given): 0, Br, H, H, H, H, H, 232.5-35.5°; 0, Cl, H, H, Me, H, H, 252-4°; 0, Cl, H, H, Me, Me, H, HCl monohydrate 277°; 0, Cl, H, H, Et, Et, H, 265°; 0, Cl, H, H, Me, CH2Ph, H, HCl 274.5°; 0, Cl, H, H, CH2CH2OH, H, H, HCl 228.5-9.5°; 0, Cl, H, H, CH2Ph, H, H, 215-16°; 0, Cl, H, H, 2-ClC6H4CH2, H, H, 220-3°; 0, Cl, H, H, 4-FC6H4CH2, H, H, 216-19.5°; 0, Cl, H, H, 4-MeC6H4CH2, H, H, 210-22°; 0, Cl, H, H, 4-MeOC6H4CH2, H, H, 175.5-9.5°; 0, Cl, H, H, 2,4-Me2C6H3CH2, H, H, 220-2°; 0, Cl, H, H, PhMeCH, H, H, 152-60°; 0, Cl, H, H, PhCH2CH2, H, H, 219-21.5°; 0, Cl, H, H, 3-pyridylmethyl, H, H, 2HCl 280.5-83.5°; 0, Cl, H, H, H, (R4R5 =) CH2CH2, 222.5-3.5°; 0, Cl, H, iso-Pr, Me, H, H, >300°; 0, Cl, H, iso-Pr, Me, Me, H, 238.5-40°; 0, Cl, H, iso-Pr, CH2CH2OH, H, H, HCl hemihydrate 185-6°; 0, Cl, H, iso-Pr, CH2Ph, H, H, 200.5-4.5°; 0, Cl, H, CH2CH:CH2, H, H, H, 213-14°; 0, Cl, H, CH2CH:CH2, Me, Me, H, 213-15°; 0, Cl, H, Bu, Me, Me, H, 187.5°; 0, Cl, H, cyclopropylmethyl, H, H, H, 220-1.5°; 0, Cl, Me, Me, H, H, H, 216-17°; 0, Cl, Me, Et, H, H, H, 229-30°; 0, Cl, Me, Pr, H, H, H, 214-15°; 0, Cl, Me, iso-Pr, H, H, H, 207-8°; 0, Cl, Me, iso-Pr, Me, Me, H, 209-11°; 0, Cl, Et, Et, Me, Me, H, 212-14°; 1, Cl, H, H, H, H, H, 281-2° (decompose); 1, Cl, Me, Me, H, H, H, 221° (decompose); 1, Cl, H, H, H, (R4R5 =) CH2CH2, 249-51°; 1, Cl, H, H, H, H, H, H, HCl 279-80° (decompose).
IT 1163-44-6P 1163-45-7P 1165-90-8P
1634-16-8P 2093-13-2P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
RN 1163-44-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2-chlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



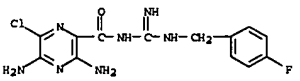
RN 1163-45-7 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[(4-methylphenyl)methyl]amino]methyl]-(9CI) (CA INDEX NAME)



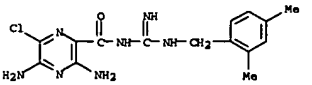
RN 1165-90-8 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[(4-methoxyphenyl)methyl]amino]methyl]-(9CI) (CA INDEX NAME)



RN 1634-16-8 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(4-fluorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



RN 2093-13-2 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2,4-dimethylphenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



L6 ANSWER 119 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1968:436172 CAPLUS
DOCUMENT NUMBER: 69:36172
TITLE: (3-Amino-2-pyrazinecarbonyl)guanidines
INVENTOR(S): Cragoe, Edward J., Jr.
PATENT ASSIGNEE(S): Merck and Co., Inc.
SOURCE: U.S., 26 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

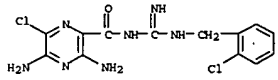
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 3313813		19670411	US 1963-313315	19621030
DE 1795438			DE	

GI For diagram(s), see printed CA Issue.

AB Title compds. I are prepared from II, III, and IV. Thus, 3318 g. SO2Cl2 is added in 30 min. to 765 g. Me 3-amino-2-pyrazinecarboxylate in 5.1 C6H6; the mixture is agitated 1 hr., refluxed 5 hrs., and agitated overnight to give 724 g. Me 3-amino-5,6-dichloropyrazinecarboxylate(V), m. 233-4° (MeCN). A mixture of 100 g. V. and 1.1 Me2SO is heated to 65° and NH3 gas is introduced into the mixture in 45 min. at 65-70°; the mixture is cooled to 10° and NH3 is introduced in 1.25 hrs. to give 91.5% Me 3,5-diamino-6-chloropyrazinecarboxylate,m. 212-13° (MeCN). Also prepared, by known methods are the following II (X, Y, Z, and m.p. given): MeO, NH2, H, 252-4° (decomposition); MeO, NH2, Br, 217-19°; MeO, NH2, iodine, 200-2°; MeO, PhNH, Cl, 171.5-73°; MeO, p-ClC6H4NH, Cl, 207-8°; MeO, Me2N, Cl, 145.5-6.5°; MeO, MeS, Cl, 214-16°; MeO, MeSO, Cl, 237.5-40.5° (decomposition); MeO, OH, Cl, apprx.245° (decomposition); MeO, OH, H, 220-60° (decomposition); MeO, NH2.H, 252-4° (decomposition); MeO, Me2N, H, 242.5-3.5°; MeO, MeO, H, 205.5-7.5°; MeO, PhCH2NH, H, 157-8°; MeO, MeO, MeO, Cl, 255-7°; MeO, MeS, Cl, 212-14°; MeO, SH, Cl, 207-8° (decomposition); MeO,EtO, Cl, Cl, 123-5°; MeO, H, Me, 138.5-40.5°; MeO, Cl, Me, 176.5-9.5°; MeO, Me2N, Me, 108.5-10.5°; MeO, Me, H, 165-7°; MeO, Me, Br, 179-81°; NH2, H, Et, 165.5-8.5°; OH, H, Et, 149-52°; MeO, H, Et, 85-7.5°; OH, cyclohexyl, H, 182.5-3.5°; MeO, cyclohexyl, H, 173-4.5°; NH2, H, cyclohexyl, -; OH, H, cyclohexyl, -; MeO, H, cyclohexyl, 126.5-8.0°; NH2, H, cyclopropyl, 185.5-7.5°; OH, H, cyclopropyl, 169-72°; MeO, H, cyclohexyl, 112.5-14.5°; MeO, Ph, H, 231-2°; MeO, H, Ph, 140-1°; MeO, Cl, Ph, 187.5-91.5°; MeO, Ph, Br, 217-21°; OH, H, p-ClC6H4, 213-15°; MeO, H, p-ClC6H4, 181.5-3.5°; MeO, Cl, Ph, 187.5-90.5°; MeO, Me2N, Ph, 167-9.5°; MeO, H, Cl, 142° (decomposition); MeO, MeHN, Cl, 221-2°; MeO, EtNH, Cl, 149-50°; MeO, PrNH, Cl, 138-40°; MeO, iso-PrNH, Cl, 125.5-6.5°; MeO, CH2:CHCH2NH, Cl, 105-6.5°; MeO, BuNH, Cl, 140-2°; MeO, sec-BuNH, Cl, 106-8°; MeO, iso-BuNH, Cl, 113.5-15.5°; MeO, tert-BuNH, Cl, 98-108°; MeO, Me(CH2)4NH, Cl, 100.5-2.5°; MeO, BuCHMeNH, Cl, -; MeO, Et2CHNH, Cl, -; MeO, Me(CH2)5NH, Cl, 72.5-5.5°; MeO, cyclopropylmethylamino, Cl, 132-3°; MeO, cyclopropylamino, Cl, 167-9°; MeO, cyclopentylamino, Cl, 119.5-21.5°; MeO, PhCH2NH, Cl, 157-8°; MeO, p-MeC6H4CH2NH, Cl, 112.5-14.5°; MeO, o-FC6H4CHNH, Cl, 171-4°; MeO, p-ClC6H4CH2NH, Cl, 136-7°; MeO, PhCH2CH2NH, Cl, 115-19°; MeO, F3CCH2NH, Cl, 153-4°; MeO, F3CCH2CH2NH, Cl, 124.5-5.5°; MeO, HOCH2CH2NH, Cl, 155-7°; MeO, HOCH2(CHOH)4CH2NH, Cl, 172-5°; MeO, H2NCH2CH2NH, Cl, 265°; MeO, Me2NCH2CH2NH, Cl, 257°; MeO, 4-pyridylmethylamino, Cl, 95-7°; Me, 2-furylmethylamino, Cl, 148-9°; MeO, MeEtN, Cl, 102-4°; MeO, MePrN, Cl, 83.5-5.5°; MeO, iso-PrMeN, Cl, 75.5-7.5°; MeO, Me(CH2:CHCH2)N, Cl, 90.5-3°; MeO, MeBun, Cl, 59.5-61.5°; MeO, Et2N, Cl, 99-101°; MeO, EtPrN, Cl, -; MeO, iso-PrEtN, Cl, -; MeO, Et(CH2:CHCH2)N, Cl, -; MeO, EtBun, Cl, 77.5-9.5°; Me, Pr2N, Cl, 68.5-71.5°; MeO, PrBuN, Cl, -; MeO, 1-pyrrolidinyl, Cl, 168-71°; MeO, hexamethylenimino, Cl, 109-11°; MeO, 4-methylpiperazino, Cl, 186-8°; MeO, MeNHNH, Cl, 136.5-8°; MeO, Me2NCH2CH2O, Cl, 134.5-6.5°; NH2, H, Cl, 227-30°; OH, H, MeSO2, 239-42° (decomposition). p-Methylbenzylamine is treated with H2NC(:NH)SMe.0.5H2SO4 to give 28% p-MeC6H4CH2NHC(:NH)NH2HCl, m. 153-5°. Similarly prepared are Me(PhCH2)NC(:NH)NH2.HCl, m. 122.5-5.5°, and the following RNHC(:NH)NH2.HCl (R and m.p. given): o-ClC6H4CH2, 131-6°; p-ClC6H4CH2, 162.5-4.5°; p-MeOC6H4CH2, 132-7°; 2,4-Me2C6H3CH2, 105-15°; 2,4-Cl2C6H3CH2, 145-8°; 3,4-Cl2C6H3CH2, 153-7°; PhCH2CH2, 135-8°; PhCH2, 175-8°. 5,6-Diaminouracil-HCl (17.9 g.) is treated at 60° with 14.9 g. cyclohexylglyoxal-0.5H2O to give 7.5 g. 7-cyclohexyllumazine [III (X = H, Y = cyclohexyl)], m. 229-31°, which is hydrolyzed to give II (X = OH, Y = cyclohexyl, Z = H). Similarly prepared are (m.p. given): III (X = Me, Y = Ph) [or III (X = Me, Y = Me)], 281.5-2.5°; III (X = Ph, Y = Me) [or III (X = Me, Y = Ph) [sic], 254.5-5.5°; II (X = OH, Y = Ph, Z = Me) [or II (X = OH, Y = Me, Z = Ph)], 193.5-4.5°; II (X = OH, Y = Me, Z = Ph) [or II (X = OH, Y = Ph, Z = Me)] [sic], 155-6°. II (X = MeO, Y = Ph, Z = Me) [or II (X = MeO, Y = Me, Z = Ph)] (m. 163-4°) and II (X = MeO, Y = Me, Z = Ph) [or II (X = MeO, Y = Ph, Z = Me)][sic] (m. 162.5-3.5°) are prepared by esterification. Methyl 3-isopropylidenamino-6-anilino-2-pyrazinecarboxylate, m. 195.5-7.5°, is prepared from Me2CO and the amine. Me 3-amino-5,6,7,8-tetrahydroquinoxaline-2-carboxylate,m. 154-5°, and Me 3-amino-7-chloroquinoxaline-2-carboxylate,m. 224.5-5.5°, are prepared by esterification. Alloxan-H2O (61.44 g.) is treated with 60 g. 3,4-(H2N)2C6H3Cl to give 33% 8-chloroalloxazine, m. 365-6°, and 42% 7-Chloroalloxazine, m. >380°, which is treated at 165° with NH3 in an autoclave to give 68% 3-amino-7-chloroquinoxaline-2-carboxylicacid, m. 191-2° (decomposition). A mixture of 33 g. II (X = NH2, Y = H, Z = Cl), 200 ml. Ac2O, and 200 ml. HC(OEt)3 is refluxed 1.5 hrs. to give 20 g. 4-hydroxy-6-chloropteridine(VI), m. 268-70° (decomposition). VI (5.5 g.) is treated with 4.4 g. PhCH2SH to give 5.5 g. 4-hydroxy-6-benzylthiopteridine(VIII), m. 233-5°. Similarly prepared is 4-hydroxy-6-methylthiopteridine, m. 289.5-91.5°. VII is heated with NaOH to give II (X = OH, Y = H, Z = PhCH2S(VIII), m. 138.9°. Similarly prepared is II (X = OH, Y = H, Z = MeS), m. 182-4° (decomposition). II (X = MeO, Y = Me2N, Z = Cl) (11.5 g.) is treated with 26.3 g. H2NC(:NH)NH2.HCl (IX) in the presence of 5.75 g. Na to give 93% (3-amino-5-dimethylamino-6-chloro-2-pyrazinecarbonyl)guanidine(X), m. 216-17°, HCl salt m. 298° (decomposition). Similarly prepared is I.HCl (R = R1 = H, X = Y = Cl) (m. 259-61°) which is treated with Me2NH to give X. II (X = MeO, Y = Me2NCH2CHO, Z = Cl) (9.4 g.) is treated with 20.0 g. IX in the presence of 4 g. Na to give 2.5 g. I.2HCl [R = R1 = H, X = NHC(:NH)NH2, Z = Cl), m. >340°. A solution of 8.5 5. VIII in 50 ml. Ac2O is heated 5 hrs. to give 6.6 g. 2-methyl-6-benzylthio-4H-pyrazine[2,3-d][1,3]oxazin-4-one[IV (X = PhCH2S)] (XI), m. 116.5-18.5°; similarly prepared is IV (X = MeS), m. 189-91°. XI (3.4 g.) is treated with 5.0 g. IX in the presence of 1.0 g. Na to give 1.1 g. I (R = R1 = X = H, Y = PhCH2S), m. 171-3° (decomposition). Also prepared, by the above or related methods, are the following I (R = R1 = H) (X, Y, and m.p. given): NH2, Br, 232.5-5.5° (decomposition). Also NH2, iodine, 273-4° (decomposition); H, MeS, 203-5°; H, MeSO2, 224-6° (decomposition); OH, H, >310°; NH2, H, 286-8°; Me2N, H, 224-5°; MeO, H, 229-30°; PhCH2NH, H, 231-3°; the following I (R = R1 = H, Y = Cl) (X and m.p. given): NH2, 240.5-1.5° (HCl salt m. 293.5°); MeNH, 238-9°; EtNH, 217-18°; PrNH, 221-2°; iso-PrNH, 215°; CH2:CHCH2NH, 213-14°; BuNH, 219.5°; sec-BuNH, 208-9°; iso-BuNH, 221°; tert-BuNH, 222-3°; Me(CH2)4NH, 215-16°; BuCHMeNH, 186.5-8.5°; Et2CHNH, 209-11°; Me(CH2)5NH, 194.5-6.5°; cyclopropylmethylamino, 220-1.5°; cyclopropylamino, 213-15°; cyclopentylamino, 219-20°; PhCH2NH, 206-9°; p-MeC6H4CH2NH, 216-17°; o-FC6H4CH2NH, 206-8°; p-ClC6H4CH2NH, 225-6°; PhCH2CH2NH, - (HCl salt m. 199-202°); F3CCH2NH, 232-3°; F3CCH2CH2NH, 221-2.5°; HOCH2CH2NH, - (HCl salt m. 272-3°); HOCH2(CHOH)4CH2NH, 223-4°; H2NCH2CH2NH, - (HCl salt m. 311°); Me2NCH2CH2NH, 192.5-4.5°; 4-pyridylmethylamino, 239-40°; 2-furylmethylamino, 217-18°; PhNH, 246.5-8.5°; p-ClC6H4NH, 276-8°; MeEtN, 229-3°; MeBuN, 214-15°; iso-PrMeN, 207-8°; Me(CH2:CHCH2)N, 207-8°; MeBuN, 208-9°; Et2N, 215°; EtPrN, 224-5°; iso-PrEtN, 207-8°; Et(CH2:CHCH2)N, 208-9°; EtBuN, 200.5-1.5°; Pr2N, 221-2°; PrBuN, 215-17°; 1-pyrrolidinyl, 244.5-5.5°; hexamethylenimino, 224-5°; 4-methylpiperazino, - (2HCl salt m; 229-300°); MeNHNH, 234°; Cl2N, - (HCl salt m. 259-61°); MeNH, 218-19° (decomposition); Me2NNMe, - (2HCl salt m. 262° (decomposition)]; MeNH, 210° (decomposition) [sic]; Me2N, 245° (decomposition); MeBrN, - (HCl salt m. 288° (decomposition)]; EtNH, 207.5-9.5° (decomposition); cyclohexylamino, 221-2° (decomposition); cycloheptylamino, 228-30° (decomposition); cyclopropylamino, 196.5-9° (decomposition); PhNH, 224-6° (decomposition); PhNH, 194.5-5.5° (decomposition)[sic]; Ph2N, 234.5-5.5°; PhClN, 214-16° (decomposition); PhBrN, 234-6° (decomposition); p-ClC6H4NH, 282-5° (decomposition); MePhN, 212-13° (decomposition); MePhN, 218-19° (decomposition)[sic]; Me2NNPh, 204-6° (decomposition); 1-pyrrolidinyl, 220-1°; 1-pyrryl, 211-13°; 3-chloro-1-pyrrolyl, 246-7° (decomposition); (3-isopropylidineamino-6-anilino-2-pyrazinecarbonyl)guanidine,214-16° (decomposition); (3-acetoamido-6-methylthio-2-pyrazinecarbonyl)guanidine,220-2°; the following I (X = NH2, Y = Cl) (R, R1, m.p., and m.p. HCl salt given): H, HOCH2CH2, -, 228.5-9.5° (decomposition); H, Ph, -, -, [MeSO3H salt m. 272° (decomposition)]; H, PhCH2, 215-16° (decomposition); -; H, p-FC6H4CH2, 216-19.5° (decomposition), -; H, PhCHMe, 153-60° (decomposition), -; H, 2-C10H7CH2, 243.5-5.5° (decomposition), -; H, 3-pyridylmethyl, 280.5-3.5° (decomposition), -; H, p-MeC6H4CH2, 210-12° (decomposition), -; Me, PhCH2, 274.5° (decomposition), -; H, o-ClC6H4CH2, 220-3° (decomposition), -; H, p-ClC6H4CH2, 204-6° (decomposition), -; H, p-MeOC6H4CH2, 175.5-9.5° (decomposition), -; H, 2,4-Me2C6H3CH2, 220-2° (decomposition), -; H, 2,4-Cl2C6H3CH2, -, 267.5-70.5° (decomposition); H, 3,4-Cl2C6H3CH2, 216-19° (decomposition), -; H, PhClH,CH2, 219-21° (decomposition), -; Me, Me, 240° (decomposition), -, [HCl.H2O salt m. 275° (decomposition)]; H, octahydrol-azocinyl, -, -; Et, Et, 265° (decomposition), -; Bu, Bu, 148-9°, -; (RR1 =) (CH2)4, -, -; (RR1 =) 3-oxapentamethylene, -, -; the following I (R = R1 = Me, Y = Cl) (X and m.p. given): iso-PrNH, 238-40.5°; CH2:CHCH2NH, 213-15°; BuNH, 187.5°; cyclopropylmethylamino, 196-7°, Me2N, 219°; MeEtN, 217-18°; iso-PrMeN, 209-11°; Et2N, 212-14°; I (R = H, R1 = HOCH2CH2, X = iso-PrNH, Y = Cl).HCl.0.5H2O [m. 185-6° (decomposition)], and 1-(3,5-diamino-6-chloro-2-pyrazinecarbonyl)2,3-dimethylguanidine.

IT 1163-44-6P 1163-45-7P 1165-90-8P
1166-01-4P 1634-16-8P 1636-56-2P
2088-58-6P 2093-13-2P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

RN 1163-44-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2-chlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



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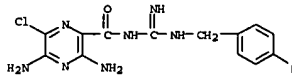

RN 1165-90-8 CAPLUS
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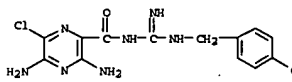

RN 1166-01-4 CAPLUS
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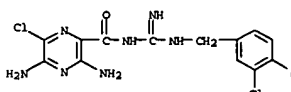

RN 1634-16-8 CAPLUS
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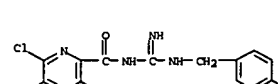
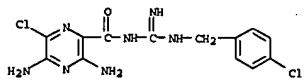
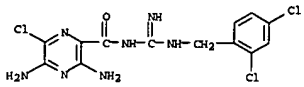


RN 1636-56-2 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[(p-chlorobenzyl)amidino]-(7CI, 8CI) (CA INDEX NAME)

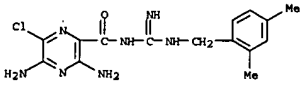


RN 2088-58-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2,4-dichlorophenyl)methyl]amino]iminomethyl]-,monohydrochloride (9CI) (CA INDEX NAME)



● HCl

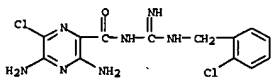
RN 2093-13-2 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2,4-dimethylphenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



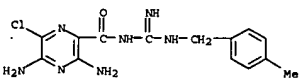
L6 ANSWER 120 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1968:49653 CAPLUS
DOCUMENT NUMBER: 68:49653
TITLE: Derivatives of pyrazine
INVENTOR(S): Pollak, Peter I.; Tull, Roger J.
PATENT ASSIGNEE(S): Merck and Co., Inc.
SOURCE: U.S., 4 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 3328404		19670627	US 1966-574904	19660825
FR 1525691			FR	
GB 1173342			GB	
ZA 6703249		19670000	ZA	

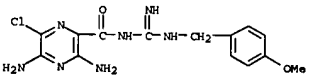
GI For diagram(s), see printed CA Issue.
AB (3,5-Diamino-6-halopyrazinoyl)guanidineand (3,5-diamino-6-halopyrazinamido)guanidinecompds. of structure I possess diuretic properties and selectively enhance the excretion of Na and Cl and suppress the excretion of K. Thus, 0.1 mole II (R = R1 = R2 = H, R3 = Me) (IIa) heated 12 hrs. at 100° in 200 ml. liquid NH3 gives 90% 3,5-diamino-6-chloropyrazinamide(III), m. 218.5-20.6° (MeOH) (Step A). III (0.0115 mole) in 20 ml. HCONMe2 and 2 ml. POCl3 heated 10 min. at 80° gives 77% 3,5-diamino-6-chloropyrazinonitrile,m. 295° (H2O), which (1 mole) in 1.1 moles absolute EtOH and 500 ml. Et2O is saturated with 1.1 moles HCl gas at 0° and kept 4 days at 0°. The formed Et 3,5-diamino-6-chloropyrazinimidate-HClis heated 16 hrs. at 40° in 1 l. EtOH with 2 moles HNMe2 to give N,N-dimethyl-3,5-diamino-6-chloropyrazinamidine. This is refluxed 1 hr. with 1 mole guanidine in EtOH, the mixture evaporated, and the residue refluxed 5 hrs. in 500 ml. 2N HCl ,to give (3,5-diamino-6-chloropyrazinoyl)guanidine-HCl,m. 293.5° (decomposition). (Step B). The 6-bromo analog is prepared similarly the as free base, m. 232.5-5.5°. Replacing guanidine by aminoguanidine in B gives (3,5-diamino-6-chloropyrazinamido)guanidine,m. 281-2° (decomposition). (Step C). Replacing IIa in A by Me 3-amino-5-dimethylamino-6-chloropyrazinoateand following the other steps gives (3-amino-5-dimethylamino-6-chloropyrazinamido)guanidine,m. 221° (decomposition). Replacing aminoguanidine by 1-amino-3,3-dimethylguanidine in C gives 1-(3,5-diamino-6-chloropyrazinamido)-3,3-dimethylguanidine-HCl, m. 279-80° (decomposition). With these methods and using the appropriate Me 3-amino-5-NR1R2-substituted-6-chloropyrazinoate and the appropriate guanidine the following I (R = Cl, R5 = H) are prepared [R1, R2, R3, R4, and m.p. (all with decomposition) given]:
H, H, Me, H, 252-4°; H, H, Me, Me, - (HCl.H2O salt m. 277°); H, H, Et, Et, 265°; H, H, Me, PhCH2, - (HCl salt m. 274.5°); H, H,CH2CH2OH, H, - (HCl salt m. 228.5-9.5°); H, H, PhCH2, H, 215-16°; H, H, o-ClC6H4CH2, H, 220-3°; H, H, p-FC6H4CH2,H, 216-19.5°; H, H, p-MeC6H4CH2, H, 210-12°; H, H, p-MeOC6H4CH2, H, 175.5-9.5°; H, H, 2,5-Me2C6H3CH2, H, 220-2°, H, H, PhCHMe, H, 152-60°; H, H, PhCH2-CH2, H, 219-21.5°; H, H, 3-pyridylmethyl, -H (di-HCl salt m. 280.5-3.5°); H, H, H, (R4R5 = CH2CH2, 222.5-23°; H, iso-Pr, Me, H, >300°; H, iso-Pr, Me, Me, 238.5-40°; H, iso-Pr, CH2CH2OH, H, -(HCl.0.5H2Osalt m. 185-6°); H, iso-Pr, PhCH2, H, 200.5-4.5°; H, CH2:CHCH2, H, H, 213-14°; H, CH2:CHCH2, Me, Me, 213-15°; H, Bu, Me,Me, 187.5°; H, cyclopropylmethyl, H, H, 220-1.5°; Me, Me, H, H, 216-17°; Me, Et, H, H, 229-30°; Me, Pr, H, H, 214-15°; Me, iso-Pr, H, H, 207-8°; Me, iso-Pr, Me, Me, 209-11°; Et, Et, Me, Me, 212-14°.
IT 1163-44-6P 1163-45-7P 1165-90-8P 1634-16-8P 2093-13-2P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
RN 1163-44-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2-chlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



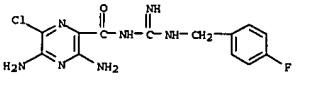
RN 1163-45-7 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[(4-methylphenyl)methyl]amino]methyl]-(9CI) (CA INDEX NAME)



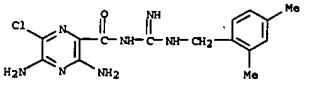
RN 1165-90-8 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[(4-methoxyphenyl)methyl]amino]methyl]-(9CI) (CA INDEX NAME)



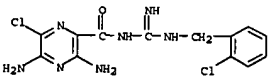
RN 1634-16-8 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(4-fluorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



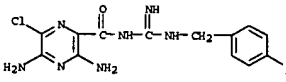
RN 2093-13-2 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2,4-dimethylphenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



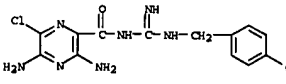
L6 ANSWER 121 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1967:37887 CAPLUS
DOCUMENT NUMBER: 66:37887
TITLE: Pyrazine diuretics. II. N-amidino-3-amino-5-substituted 6-halopyrazinecarboxamides
AUTHOR(S): Cragoe, Edward J., Jr.; Woltersdorf, Otto W., Jr.; Bicking, John B.; Kwong, Sara F.; Jones, James Holden
CORPORATE SOURCE: Div. of Merck and Co., Inc., Merck Sharp and Dohme Res. Labs., West Point, PA, USA
SOURCE: Journal of Medicinal Chemistry (1967), 10(1), 66-75
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 66:37887
GI For diagram(s), see printed CA Issue.
AB The synthesis of a series of N-amidino-3-amino-5-substituted-6-halopyrazinecarboxamides (I) is described In rats and dogs, these compds. cause diuresis and saluresis while K excretion is unaffected or repressed Compds. with a variety of 5 substituents including hydroxy, alkoxy, mercapto, alkylmercapto, amino, and substitute amino were prepared The latter 2 types embrace compds. with the highest activity. Several routes for the synthesis of Me 3-amino-5,6-dichloropyrazinoate,a key intermediate, are presented. 23 references.
IT 1163-44-6P 1163-45-7P 1165-90-8P 1166-01-4P 1634-16-8P 1636-56-2P 2088-58-6P 2093-13-2P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
RN 1163-44-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2-chlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



RN 1163-45-7 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[(4-methylphenyl)methyl]amino]methyl]-(9CI) (CA INDEX NAME)



RN 1165-90-8 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[(4-methoxyphenyl)methyl]amino]methyl]-(9CI) (CA INDEX NAME)



RN 1166-01-4 CAPLUS
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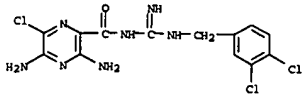
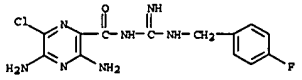
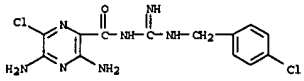


RN 1634-16-8 CAPLUS

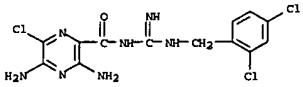
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(4-fluorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



RN 1636-56-2 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[(p-chlorobenzyl)amidino]-(7CI, 8CI) (CA INDEX NAME)

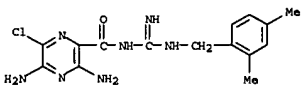


RN 2088-58-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2,4-dichlorophenyl)methyl]amino]iminomethyl]-,monohydrochloride (9CI) (CA INDEX NAME)



● HCl

RN 2093-13-2 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2,4-dimethylphenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



L6 ANSWER 122 OF 122 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1965:82636 CAPLUS
DOCUMENT NUMBER: 62:82636
ORIGINAL REFERENCE NO.: 62:14698f-h,14699a-h,14700a-h,14701a-h,14702a-b
TITLE: Substituted guanidines
INVENTOR(S): Cragoe, Edward J., Jr.
PATENT ASSIGNEE(S): Merck & Co., Inc.

SOURCE: 99 pp.
DOCUMENT TYPE: Patent
LANGUAGE: Unavailable
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
BE 639386		19640430	BE	
			US	19621030

PRIORITY APPLN. INFO.:

GI For diagram(s), see printed CA Issue.

AB A suspension of 765 g. Me 3-aminopyrazinecarboxylate in 5 l. C6H6 was treated with 1.99 l. SO2Cl2, refluxed for 5 hrs., and left overnight at room temperature to give 888 g. crude Me 3-amino-5,6-dichloropyrazinecarboxylate (I), m. 233-4°. Into a solution of 100 g. I in 1 l. dry Me2SO dry NH3 was passed under stirring at 65-70° for 45 min., then at 10° for 1.25 hrs. to give 82.5 g. Me 3,5-diamino-6-chloropyrazinecarboxylate (II), m. 212-13°. A mixture of 14.2 g. II, 9 g. Pd-C, 4 g. MgO, and 250 ml. MeOH was shaken under H for 18 hrs. at room temperature to give Me 3,5-diaminopyrazinecarboxylate (III), m. 252-4° (decomposition) (iso-PrOH). Bromination of a suspension of 2 g. III in 25 ml. AcOH at 50° with 2.1 g. Br in 10 ml. AcOH gave 1.2 g. Me 3,5-diamino-6-bromopyrazinecarboxylate (IV), m. 217-19°. Hg(OAc)2 (3.2 g.) and a solution of 2.5 g. iodine in 20 ml. warm dioxane was added rapidly to a suspension of 1.7 g. III in 30 ml. H2O at 70°, the mixture heated for 5 min., cooled to room temperature, and treated with 50 ml. 15% KI solution precipitated 1.2 g. Me 3,5-di-amino-6-iodopyrazinecarboxylate, m. 200-2°. I (11.1 g.), 500 ml. iso-PrOH, 14.4 g. PhNH2, and 12.8 g. PhNH2.HCl was refluxed 24 hrs. under stirring to give 10 g. Me 3-amino-5-anilino-6-chloropyrazinecarboxylate, m. 171.5-73° (iso-PrOH). Similarly were prepared Me 3-amino-5-(p-chloroanilino)-6-chloropyrazinecarboxylate, m. 207-8° (MeCN), and Me 3-amino-5-dimethylamino-6-chloropyrazinecarboxylate (V), m. 145.5-6.5° (MeOH). A solution of 10 g. MeSH in 17 ml. 20% NaOH and 100 ml. MeOH was added to a boiling mixture of 17.7 g. I and 1 l. MeOH and refluxed 15 min. to precipitate 12 g. Me 3-amino-5-methylthio-6-chloropyrazinecarboxylate (VI), m. 212-16° (MeOH). VI (23.4 g.), 35 ml. 30% H2O2, and 300 ml. AcOH was stirred 18 hrs. at room temperature to give 18.5 g. the 5-methylsulfinyl analog (VII), m. 237.5-40.5° (decomposition) (MeOH-AcOEt-HCONH2). Hydrolysis of 7.5 g. VII in 75 ml. AcOH and 12 ml. H2O on a steam bath for 3 hrs. produced 3.7 g. Me 3-amino-5-hydroxy-6-chloropyrazinecarboxylate (VIII), m. .apprx.245° (decomposition) (HCONH2-EtOH). Hydrogenation of VIII with Pd-C and MgO at room temperature resulted in Me 3-amino-5-hydroxypyrazinecarboxylate, decompose 320-60°. Also were prepared Me 3-amino-5-dimethyl-aminopyrazinecarboxylate, m. 242.5-3.5°, Me 3,5-diaminopyrazinecarboxylate, m. 252-4° (decomposition), and Me 3-amino-5-methoxypyrazinecarboxylate, m. 205.5-7.5°. A mixture of 8.9 g. I and 20 ml. PhCH2NH2 was heated on a steam bath for 30 sec. to give 7.5 g. Me 3-amino-5-benzylamino-6-chloropyrazinecarboxylate (IX), m. 157-8° (MeOH). Hydrogenation of IX yielded Me 3-amino-5-benzylaminopyrazinecarboxylate, m. 189.5-91.5°. Treatment of 1.1 g. I with MeONa in 200 ml. boiling absolute MeOH produced 1 g. Me 3-amino-5-methoxy-6-chloropyrazinecarboxylate, m. 255-7° (MeCN). Na2S (9.6 g.) and 10 g. S was refluxed in 80 ml. absolute EtOH. Addition of 8.9 g. I at 25° and stirring for 1 hr. gave 7.8 g. Me 3-amino-5-mercapto-6-chloropyrazinecarboxylate, m. 207-8° (decomposition). To a refluxing solution of 4.44 g. I in 300 ml EtOH was added guanidine (from 1.98 g. guanidine-HCl) in 50 ml. absolute EtOH in 15 min. and the mixture refluxed 0.5 hr. to give 3.1 g. Me 3-amino-5-ethoxy-6-chloropyrazinecarboxylate, m. 123-5° (iso-PrOH).

3-Amino-6-methylpyrazinoylamide (31 g.) was heated 10 min. with 320 ml. 10% NaOH. The resulting Na salt of the acid (97 g.) was methylated with 77 g. Me2SO4 in 700 ml. MeOH 19 hrs. at room temperature to give 18 g. Me 3-amino-6-methylpyrazinecarboxylate (X), m. 138.5-40.5° (C6H6). Chlorination of 9.2 g. X with 65 ml. SO2Cl2 under cooling produced 4.4 g. Me 3-amino-5-chloro-6-methylpyrazinecarboxylate, m. 108.5-10.5° (C6H6-cyclohexane). A mixture of 30 g. 3-amino-5-methylpyrazinecarboxylic acid and a solution of 30% HCl in 650 ml. MeOH was stirred 42 hrs. at room temperature to give 15.4 g. Me 3-amino-5-methylpyrazinecarboxylate (XI), m. 165-7° (H2O). A solution of 4.18 g. Br in 3 ml. AcOH was added to a solution of 4.2 g. XI in 15 ml. AcOH in 20 min. to produce 3.6 g. Me 3-amino-5-methyl-6-bromopyrazinecarboxylate, m. 179-81°. Aminomalonamidamidine-2HCl (52.5 g.) was added to an ice-cooled solution of 28.8 g. ethylglyoxal in 450 ml. H2O. The mixture was made alkaline with .apprx.65 ml. concentrated NH4OH and left 20 hrs. at room temperature to precipitate 17.5 g. 3-amino-6-ethylpyrazinecarboxamide, m. 165.5-8.5° (iso-PrOH), which was saponified 30 min. on a steam bath with 10% NaOH to give 3-amino-6-ethylpyrazinecarboxylicacid (XII), m. 149-52°. Stirring 14 g. XII in a solution of 33% HCl in 160 ml. MeOH 24 hrs. at room temperature gave 4.3 g. XII Me ester, m. 85-7° (iso-PrOH). Also prepared were 3-amino-6-p-chlorophenylpyrazinecarboxylicacid, m. 207-13°, and its Me ester, m. 181.5-3.5°. To a suspension of 17.9 g. 5,6-diaminouracil in 250 ml. H2O at 60° 14.9 g. cyclohexylgiyoxal-0.5 H2O was added and the mixture heated 1 hr. on a steam bath to give 7.5 g. 7-cyclohexyllumazine (XIII), m. 229-31° (aqueous AcOH). A solution of 18.5 g. XIII and 9 g. NaOH in 90 ml. H2O was heated in an autoclave 17 hrs. at 105° to give 8 g. 3-amino-5-cyclohexylpyrazinecarboxylicacid, m. 182.5-3.5° (aqueous iso-PrOH); Me ester m. 173-4.5°. Similarly were prepared Me 3-amino-6-cyclohexylpyrazinecarboxylate, m. 126.5-28°, Me 3-amino-6-cyclopropylpyrazinecarboxylate, m. 112.5-14.5° (amide m. 185.5-7.5°, free acid m. 169-72°), Me 3-amino-5-phenylpyrazinecarboxylate (XIV), m. 231-2°, and Me 3-amino-6-phenylpyrazinecarboxylate (XV), m. 140-1°. Chlorination of 25.6 g. XV with 90 ml. SO2Cl2 1.5 hrs. at room temperature gave Me 3-amino 5-chloro-6-phenylpyrazinecarboxylate, m. 187.5-91.5° (AcOH). Bromination of 10.5 g. XIV in 700 ml. AcOH with 11.2 g. Br 21 hrs. at 85° gave 10.5 g. Me 3-amino-5-phenyl-6-bromopyrazinecarboxylate, m. 217-21° (AcOH). To a suspension of 103.59 g. 4,5-diamino-2,6-dihydroxypyrimidine in 1500 ml. H2O and 500 ml. concentrated NH4OH at 60° 103.71 g. 1-phenyl-1,2-propanedione was added and the mixture heated at 90° under vigorous stirring to give 82.4 g. 6(or 7)-methyl-7(or 6)-phenyllumazine, m. 281.5-2.5° (AcOH), and 32 g. 6(or 7)-phenyl-7(or 6)-methyllumazine (XVI), m. 254.5-5.5°. Saponification of XVI with 8% NaOH in an autoclave 3.5 hrs. at 170° gave 3-amino-5(or 6)-phenyl-6(or 5)-methylpyrazinecarboxylicacid, m. 193.5-4.5°; Me ester m. 163-4° (MeOH). Similarly were prepared 3-amino-5(or 6)-methyl-6(or 5)-phenylpyrazine carboxylic acid, m. 155-6°; Me ester m. 162.5-3.5° (MeOH). Me 3-amino-6-phenylpyrazinecarboxylate was chlorinated with SO2Cl2 to give Me 3-amino-5-chloro-6-phenylpyrazinecarboxylate, m. 187.5-90.5° (AcOH), and subsequently treated with Me2NH in MeOH to give Me 3-amino-5-dimethylamino-6-phenylpyrazinecarboxylate, m. 167.5-9.5° (MeOH). To 750 ml. AcOH and 3180 ml. H2O at 38°, 90 g. Me 3-aminopyrazinecarboxylate was added and Cl passed through in 25 min. to give Me 3-amino-6-chloropyrazinecarboxylate (XVII) m. 142° (decomposition) (H2O). A solution of 18.8 g. XVII, 15 g. PhNH2, and 2.5 ml. concentrated HCl in 150 ml. Me2CO was refluxed 16 hrs. to give 7.4 g. Me 3-isopropylideneamino-6-anilinopyrazinecarboxylate, m. 195.5-7.5° (iso-PrOH). A mixture of 9.3 g. 3-amino-5,6,7,8-tetrahydroquinoxaline-2-carboxylicacid and 230 ml. absolute MeOH of 10° was treated with 30 ml. concentrated H2SO4 in 1 hr. and left 24 hrs. at room temperature to give 1.6 g. the Me ester, m. 154-5° (1:5 MeOH-H2O). A solution of 60 g. 4-chloro-ω-phenylenediamine in 60 ml. H2O and 50 ml. 12N HCl was treated with a solution of 61.44 g. alloxan-H2O in 100 ml. H2O and stirred 1 hr. at 90° to give a precipitate of 78.4 g. 8-chloroalloxazine, m. 365-6° and 40.36 g. 7-chloro-alloxazine, (XVIII) m. 380° (Me2SO). A mixture of 44.2 g. XVIII and 190 ml. concentrated NH4OH was heated in an autoclave 10 hrs. at 165° to give 27.2% 3 amino-7-chloroquinoxalin-2-carboxylicacid, m. 191-2° (decomposition); Me ester m. 224.5-5.5° (MeCN). Also prepared are the following XIX (R, R1, % yield, and m.p. given): Me, H, 88, 221-2°; Et, H, 89, 149-50°; Pr, H, 75, 138-40°; iso-Pr, H, 70, 125.5-6.5°; CH2:CHCH2, H, 69, 105-6.5°; Bu, H, 91, 140-2°; sec-Bu, H, 75, 106-8°; iso-Bu, H, 51, 113.5-15.5°; tert-Bu, H, 38, 98-108°; Am, H, 72, 100.5-2.5°; MePrCH, H, --, --; Et2CH, H, --, --; C6H13, H, 70, 72.5-5.5°; cyclopropylnethyl, H, 78, 132-3° cyclopropyl, H, 98, 167-9°; cyclopentyl, H, 93, 119.5-21.5°; PhCH2, H, 64, 157-8°; p-MeC6H4CH2, H, 66, 112.5-14.5°; o-FC6H4CH2, H, 84, 171-4°; p-ClC6H4CH2, H, 93, 136-7°; PhCH2CH2, H, 59, 115-19°; CF3CH2, H, 97, 153-4° CF3CH2CH2, H, 76, 124.5-5.5°; HOCH2CH2, H, 100, 155-7°; HOCH2(CHOH)4CH2, H, 60, 172-5°; NH2CH2CH2, H, 96, 265°; Me2NCH2CH2, H, 40, 257°; 4-pyridylmethyl, H, 69, 95-7°; 2-furylmethyl, H, 81, 148-9°; Me, Et, 73, 102-4°; Me, Pr, 58, 83.5-5.5°; Me, iso-Pr, 78, 75.5-7.5°; Me, CH2:CHCH2, 70, 90.5-92°; Me, Bu, 74, 59.5-61.5°; Et, Et, 54, 99-101°; Et, Pr, --, --; Et, iso-Pr, --, --; Et, CH2:CHCH2, --, --; Et, Bu, 91, 77.5-9.5°; Pr, Bu, --, --; Pr, Pr, 66, 68.5-71.5°; (NRR1 =) pyrrolidino, 95, 168-71°; (NRR1 =) 1 (hexahydroazepinyl), 75, 109-11°; (NRR1 =) N'-Methylpiperazino, 88, 186-8°; Me, NH2, 67, 136.5-38° Guanidine-HCl (XX) (26.3 g.) was added to a solution of MeONa (5.75 g. Na in 150 ml. absolute MeOH), the precipitated NaCl filtered off, and the filtrate concentrated to 30 ml. After addition of 11.5 g. V the mixture was boiled 1 min., then maintained 1 hr. at room temperature to give 93% (3-amino-5-dimethylamino-6-chloropyrazinecarbonyl)guanidine (XXa), m. 216-17°; HCl salt m. 298° (decomposition). Similarly were prepared (3,5-diamino-6-bromopyrazin-carbonyl)guanidine, m. 232.5-5.5° (decomposition), (3,5-diamino-6-iodopyrazinecarbonyl)guanidine-HCl, m. 273-4° (decomposition) and (3-isopropylideneamino-6-anilinopyrazinecarbonyl)guanidine m. 214-16° (decomposition). To a solution of 920 mg. Na in 50 ml. absolute iso-PrOH 3.85 g. XX was added and the NaCl filtered off. Adding 4.4 g. I and refluxing the mixture 15 min. gave (3-amino-5,6-dichloropyrazinecarbonyl)guanidine HCl salt (XXb) m. 259-61°. The solution of XXb in 5 ml. HCONMe2 was treated with 1 ml. 25% aqueous Me2NH 1 hr. on a steam bath to give XXa. Reaction of 11.1 g. I with 55 ml. Me2NCH2CH2OH 20 min. on a steam bath gave 9.5 g. Me 3-amino-5-(2-dimethylamino-ethoxy)-6-chloropyrazinecarboxylate (XXI), m. 134.5-6.5° (C6H6-cyclohexane). To 20 g. XX in iso-PrONa (4 g. Na in 100 ml. iso-PrOH) 9.4 g. XXI was added and the mixture heated 30 min. on a steam bath to give 2.5 g. (3-amino-5-guanidino-6-chloropyrazinecarbonyl)guanidine-2HCl, m. >340°. A mixture of 2 l. concentrated NH4OH and 300 g. XVIII was stirred 16 hrs. at room temperature to give 260 g. 3-amino-6-chloropyrazinecarboxamide (XXII), m. 227-30°. HC(OEt)3 (200 ml.) and 33 g. XXII refluxed in 200 ml. Ac2O 1.5 hrs. gave 20 g. 4-hydroxy-6-chloropteridine (XXIII), m. 268-70° (decomposition) (iso-PrOH). A solution of 5.5 g. XXIII and 4.4 g. PhCH2SH in 100 ml. 4% NaOH was heated 30 min. on a steam bath to give 5.5 g. 4-hydroxy-6-benzylthiopteridine, m. 233-5° (aqueous iso-PrOH), which was converted into 3-amino-6-benzylthiopyrazinecarboxylicacid (XXIV), m. 138-9°, by 8 hrs. hydrolysis with 5% NaOH. XXIV (8.5 g.) in 50 ml. Ac2O was heated 5 hrs. on a steam bath to give 6.6 g. 2-methyl-6-benzylthio-4H-pyrazino[2,3-d][1,3]oxazin-4-one (XXV), m. 116.5-18.5° (C6H6). To 1 g. Na in 30 ml. iso-PrOH 5 g. XX and 3.4 g. XXV were added to give, after 1 hr. at room temperature, 1.1 g. (3-amino-6-benzylthiopyrazinecarbonyl-guanidine, m. 171-3° (decomposition). Similarly were prepared 4-hydroxy-6-methylthiopteridine, m. 289.5-91.5° (aqueous iso-PrOH),

3-amino-6-methylthiopyrazinecarboxylicacid (XXVI), m. 182-4° (decomposition) (AcOEt), 2-methyl-6-methylthio-4H-pyrazino[2,3-d][1,3]oxazin-4-one, m. 189-91° (C6H6), and 3-acetamido-6-methylthiopyrazinecarbonyl)guanidine(XXVII), m. 220-2°. Addition of HCl to XXVII in H2O gave 86% (3-amino-6-methyl-thiopyrazinecarbonyl)guanidine,m. 203-5°. A solution of 0.92 g. XXVI in 15 ml. 2.5% NaOH was treated with 1.05 g. KMnO4 in 35 ml. H2O to give 0.5 g. 3-amino-6-methylsulfonylpyrazine-carboxylicacid, m. 239-42° (decomposition) (iso-PrOH), which gave, after 5 hrs. heating in Ac2O, 2-methyl-6-methylsulfonyl-4H-pyrazino[2,3-d][1,3]oxazin4-onem. 214-16° (Me2CO), transformed into 27% 3-amino-6-methylsulfonylpyrazinecarbonyl)guanidine,m. 224-6° (decomposition) (iso-PrOH). Similarly are prepared the following XXVIIa (R, R1, % yield, and m.p. given): H, H, 93, 240.5-1.5°; 293.5° (HCl salt); Me, H, 89, 238-9°; Et, H, 63, 217-18°; Pr, H, 93,221-2°; iso-Pr, H, 75, 215°; CH2:CHCH2, H, 84, 213-14°; Bu, H, 65, 219.5°; Me-ETCH, H, 74, 208-9°; iso-Bu, H, 76, 221°; tert-Bu, H, 84, 222-3°; Am, H, 70, 215-16°; MePrCH, H, 89, 186.5-8.5°; Et2CH, H, 82, 209-11°; C6H13, H, 100, 194.5-6.5°; cyclopropylmethyl, H, 95, 220-1°; cyclopropyl, H, 85, 213-15°; cyclopentyl, H 65, 219-20°; PhCH2, H, 44, 206-9°; p-MeC6H4CH2, H, 57, 216-17°; o-PC6H4CH2, H, 100, 206-8°;. p-ClC6H4CH2, H, 96, 225-6°; PhCH2CH2, H, 57, 199-202°; CF3CH2, H, 77, 232-3°; CF3CH2CH2, H, 65, 221-2.5°; HO-CH2CH2, H, 63, 272-3°; HOCH2(CHOH)4CH2, H, 68, 223-4°; NH2CH2CH2, H, 68, 311°; Me2NCH2CH2, H, 98, 192.4-4.5°; 4-pyridylmethyl, H, 64, 239-40°; o-furylmethyl, H, 92, 217-18°; Ph, H, 95, 246.5-8.5°; p-ClC6H4, H, 95, 276-8°; Me, Et, 92, 229-30°; Me, Pr, 97, 214-15°; Me, iso-Pr, 70, 207-8°; Me, CH2:CHCH2, 95, 207-8°; Me, Bu, 95, 208-9°; Et, Et, 75, 215°; Et, Pr, 92, 224-5°; Et, iso-Pr, 75, 207-8°; Et, CH2:CHCH2, 92, 208-9°; Et, Bu, 98, 200.5-1.5°; Pr, Pr, 100, 221-2°; Pr, Bu, 84, 215-17°; (NRR1 =) pyrrolidino, 90, 244.5-5.5°; (NRR1 =) 1-hexahydroazepinyl, 49, 224-5°; (NRR1 =) N-methylpiperazino, 74, 299-300°; Me, NH2, 92, 234°.

Also prepared are the following XXVIIb (X, Y, % yield, and m.p. base and m.p. HCl salt given): H, HO, 10, >310° (decomposition); H, NH2, 8, 286-8° (decomposition), --; H, NMe2, 45, 224-5° (decomposition), --; H, MeO, 52, --, 229-30° (decomposition); H, PhCH2NH, 56, --, 231-7° (decomposition); Cl, MeO, 90, --, 257°; Cl, MeS, 100, 234.5-6.5°, --; Cl, HO, 24, --, >300° (decomposition); Cl, SH, 100, 236.5° --; Cl, EtO, 81, 215-16° --; Cl, Cl, 72, --, 259-61°; Me, H, 87, 218-19 (decomposition), --; Me, Me2N, 42, --, 262° (decomposition) (di-HCl); H, Me, 13,210° (decomposition), --; Me, Me, 38, 245° (decomposition), --; Br, Me, 35, 288° (decomposition), --; Et, H, 53, 207.5-9.5° (decomposition), --; H, cyclohexyl, 71, 221-2° (decomposition), --; cycloheptyl, H, 61, 228-30° (decomposition), --; cyclopropyl, H, 61, 196.5-99° (decomposition), --; H, Ph, 51, 224-6° (decomposition); Ph, H, 34, 194.5-5.5° (decomposition), --; Ph, Ph, 87, 234.5-5.5°, --; Ph, Cl, 69, 214-16° (decomposition), --; Br, Ph, 66, 234-6° (decomposition), --; p-ClC6H4, H, 70, 282-5° (decomposition), --; Me (or Ph), Ph (or Me), 77, 212-13° (decomposition), --; Ph (or Me), Me (or Ph) 90, 218-19° (decomposition), --; Ph, Me2N, 40, 205-6° (decomposition), --; (XY =)(CH2)4, 29, 220-1°, --; (XY =) CH:CHCH:CH, 56, 211-13°, --; (XY =) HC:CClCH:CH, 70, 246-7° (decomposition), --. A solution of 13.9 g. 2-methyl-2-pseudothiuroniumsulfate (XXVIII) and 9.2 g. H2NCH2CH2OH in 40 ml. H2O was heated 20 min. to give 12.5 g. (2-hydroxyethyl)guanidine sulfate, m. 127.5-35.5°, which was added to a solution of 2g. Na in 25 ml. MeOH, MeOH distilled, and the residue treated with 4.1 g. II 5 min. on steam bath to give 1.2 g. 1-(3,5-diamino-6-chloropyrazinoyl)-3-(2-hydroxyethyl)guanidine-HCl, m. 228.5-9.5° (aqueous iso-PrOH).

1-(3-Amino-5-isopropylamino-6-chloropyrazinoyl)-3-(2-hydroxyethyl)guanidine-HCl.0.5H2O, m. 185-6° (decomposition), was prepared from Me 3-amino-5-isopropylamino-6-chloropyrazinecarboxylate. A mixture of 6.1 g. II, 6.8 g. phenylguanidine, and 3 ml. iso-PrOH was heated 6 hrs. to give 1-(3.5-diamino-6-chloropyrazinoyl)-3-phenylguanidine,isolated as the MeSO3H salt, m. 272° (decomposition) (H2O). Ph-CH2NH2 (80.3 g.) and 69.5 g. XXVIII in 200 ml. H2O kept 18 hrs. at room temperature gave benzylguanidine sulfate, which was converted into the HCl salt (XXIX) (51.5 g.), m. 175-8° (aqueous EtOH), by treating its aqueous solution with aqueous BaCl2. To a solution of 1 g. Na in 30 ml. iso-PrOH 9.3 g. XXIX was added and half the volume distilled Addition of 2 g. II and heating the mixture 15 min. yielded 1 g. 1-(3,5-diamino-6-chloropyrazinoyl)-3-benzylguanidine,m. 215-16° (decomposition) (aqueous iso-PrOH). With the appropriate starting materials the following 3-substituted 1-(3,5-diamino-6-chloropyrazinoyl]guanidineswere prepared [3-substituent and m.p. (decomposition) given]: p-fluorobenzyl 216-19.5°; α-methylbenzyl 153-60°; 3-pyridylmethyl, 280.5-3.5°; 2-naphthylmethyl 243.5-5.5°. Also prepared were the following RR1-NC(:NH)NH2.HCl (R, R1, % yield, and m.p. given): p-Me-C6H4CH2 H, 28, 153-5°; o-ClC6H4CH2, Me, 32, 122.5-5.5°; PhCH2, H, 71, 131-6°; p-ClC6H4CH2, H, 55, 162.5-4.5°; p-MeOC6H4CH2, H, 69, 132-7°; 2,4-Me2C6H3CH2, H, 52, 105-15°; 2,4-Cl2C6H3CH2, H, 67, 145-8°; 3,4-Cl2C6H4CH2, H, 77, 155-7°; PhCH2CH2, H, 71, 135-8°.

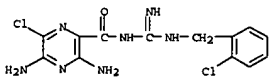
Also prepared were the following XXIXa (R, R1, % yield, and m.p. (decomposition)given): p-MeC6H4CH2, H, 27, 210-12°; PhCH2, Me, 35, 274.5° (HCl salt); o-ClC6H4CH2, H, 39, 220-3°; p-ClC6H4CH2, H, 46, 204-6° p-MeOC6H4CH2, H, 27, 175.5-9.5°; 2,4-Me2C6H3CH2 H, 59, 220-2°; 2,4-Cl2C6H3CH2, H, 30, 267.5-70.5° (HCl salt); 3,4-Cl2C6H3CH2, H, 47, 216-19°; PhCH2CH2, H, 46, 219-21.5°. To a solution of 2.3 g. Na in 200 ml. absolute MeOH 15 g. dimethyl-guanidine sulfate was added, the mixture refluxed 1 hr. and cooled, Na2SO4 filtered off, the solution concd, to 30 ml., 10.15 g. II added, and the mixture heated 30 min. and kept 1 hr. at room temperature to give 3.6 g. 1-(3,5-diamino-6-chloropyrazinoyl)-3,3-dimethyl-guanidine (XXX), decomposing at 240° HCl salt m. 275° (decomposition). To a solution of 36.57 g. Et2NH in 100 ml. H2O and 41 ml. concentrated HCl adjusted, with 3.66 g. Et2NH to pH 9.2 a solution of 50% aqueous cyanamide (65.16 g.) was added dropwise at 100° in 4 hrs. After refluxing 1 hr. and standing over night at room temperature the mixture was treated with 50 ml. of 40% NaOH and CO2 passed through under cooling to give 1,1-diethylguanidine, isolated as the HCl salt (XXXI) (35 g.), m. 147-9°. Similarly, 1,1-dibutylguanidine-HCl (XXXII), m. 104.5-106° (H2O), was obtained in 86% yield. The following compds. were also prepared: 88.6% 1-(3,5-diamino-6-chloropyrazinoyl)-3,3-diethylguanidine,m. 265° (decomposition), from II and XXXI and 72% 1-(3,5-diamino-6-chloropyrazinoyl)-3,3-dibutylguanidine, m. 148-9° (iso-PrOH), from II and XXXII.

Also prepared were the following XXXIII (R, R1, % yield, and m.p. given): iso-Pr, H, 35, 238.5-40°; CH2:CHCH2, H, 39, 215°; Bu, H, 17, 187.5°; cyclopropylmethyl, H, 3, 196-7°; Me, Me, 69, 219°; Me, Et, 49, 218°; Me, iso-Pr, 61, 209-11°; Et, Et, 40,214°. The compds. are effective in the treatment of abnormal electrolyte excretion.

IT 1163-44-6P, Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[(o-chlorobenzyl)amidino]-1163-45-7P, Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[(p-methylbenzyl)amidino]-1165-90-8P, Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[(p-methoxybenzyl)amidino]-1166-01-4P, Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[(3,4-dichlorobenzyl)amidino]-1634-16-8P, Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[(p-fluorobenzyl)amidino]-1636-56-2P, Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[(p-chlorobenzyl)amidino]-2088-58-6P, Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[(2,4-dichlorobenzyl)amidino]-, hydrochloride 2093-13-2P,

Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[(2,4-dimethylbenzyl)amidino]-
RL: PREP (Preparation)
(preparation of)

RN 1163-44-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[(2-chlorophenyl)methyl]amino]iminomethyl]-(9CI) (CA INDEX NAME)



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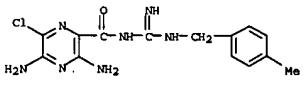

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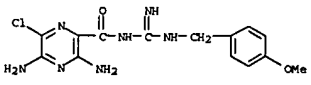

RN 1166-01-4 CAPLUS
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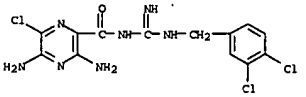

RN 1634-16-8 CAPLUS
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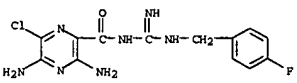

RN 1636-56-2 CAPLUS
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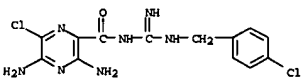

RN 2088-58-6 CAPLUS
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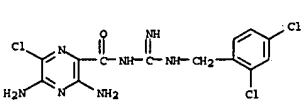

● HCl

RN 2093-13-2 CAPLUS
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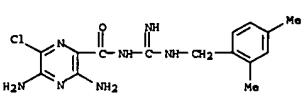

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STN INTERNATIONAL LOGOFF AT 14:13:44 ON 22 MAR 2007